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Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Campschroer T, Zhu X, Vernooij RWM, Lock MTWT

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[Intervention Review]

Alpha-blockers as medical expulsive therapy for ureteral stones

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ABSTRACT

Background

Ureteral colic is a common reason for patients to seek medical care. Alpha-blockers are commonly used to improve stone passage through so-called medical expulsive therapy (MET), but their effectiveness remains controversial. This is an update of a 2014 Cochrane review; since that time, several large randomised controlled trials (RCTs) have been reported, making this update relevant.

Objectives

To assess effects of alpha-blockers compared with standard therapy for ureteral stones 1 cm or smaller confirmed by imaging in adult patients presenting with symptoms of ureteral stone disease.

Search methods

On 18 November 2017, we searched CENTRAL, MEDLINE Ovid, and Embase. We also searched ClinicalTrials.gov and the WHO Portal/ICTRP to identify all published/unpublished and ongoing trials. We checked all references of included and review articles and conference proceedings for articles relevant to this review. We sent letters to investigators to request information about unpublished or incomplete studies.

Selection criteria

We included RCTs of ureteral stone passage in adult patients that compared alpha-blockers versus standard therapy.

Data collection and analysis

Two review authors screened studies for inclusion and extracted data using standard methodological procedures. We performed meta-analysis using a random-effects model. Primary outcomes were stone clearance and major adverse events; secondary outcomes were stone expulsion time, number of pain episodes, use of diclofenac, hospitalisation, and surgical intervention. We assessed the quality of evidence on a per-outcome basis using the GRADE approach.

Main results

We included 67 studies with 10,509 participants overall. Of these, 15 studies with 5787 participants used a placebo.

Stone clearance: Based on the overall analysis, treatment with an alpha-blocker may result in a large increase in stone clearance (risk ratio (RR) 1.45, 95% confidence interval (CI) 1.36 to 1.55; low-quality evidence). A subset of higher-quality, placebo-controlled trials suggest that the likely effect is probably smaller (RR 1.16, 95% CI 1.07 to 1.25; moderate-quality evidence), corresponding to 116 more (95% CI 51 more to 182 more) stone clearances per 1000 participants.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

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Major adverse events: Based on the overall analysis, treatment with an alpha-blocker may have little effect on major adverse events (RR 1.25, 95% CI 0.80 to 1.96; low-quality evidence). A subset of higher-quality, placebo-controlled trials suggest that alpha-blockers likely increase the risk of major adverse events slightly (RR 2.09, 95% CI 1.13 to 3.86), corresponding to 29 more (95% CI 3 more to 75 more) major adverse events per 1000 participants.

Patients treated with alpha-blockers may experience shorter stone expulsion times (mean difference (MD) -3.40 days, 95% CI -4.17 to -2.63; low-quality evidence), may use less diclofenac (MD -82.41, 95% CI -122.51 to -42.31; low-quality evidence), and likely require fewer hospitalisations (RR 0.51, 95% CI 0.34 to 0.77; moderate-quality evidence), corresponding to 69 fewer hospitalisations (95% CI 93 fewer to 32 fewer) per 1000 participants. Meanwhile, the need for surgical intervention appears similar (RR 0.74, 95% CI 0.53 to 1.02; low-quality evidence), corresponding to 28 fewer surgical interventions (95% CI 51 fewer to 2 more) per 1000 participants.

A predefined subgroup analysis (test for subgroup differences; $P = 0.002$) suggests that effects of alpha-blockers may vary with stone size, with RR of 1.06 (95% CI 0.98 to 1.15; $P = 0.16$; $I^2 = 62\%$) for stones 5 mm or smaller versus 1.45 (95% CI 1.22 to 1.72; $P < 0.0001$; $I^2 = 59\%$) for stones larger than 5 mm. We found no evidence suggesting possible subgroup effects based on stone location or alpha-blocker type.

Authors' conclusions

For patients with ureteral stones, alpha-blockers likely increase stone clearance but probably also slightly increase the risk of major adverse events. Subgroup analyses suggest that alpha-blockers may be less effective for smaller (5 mm or smaller) than for larger stones (greater than 5 mm).

PLAIN LANGUAGE SUMMARY

Alpha-blockers for ureteral stones in adult patients with symptoms of stone disease

Review question

Does medical treatment with alpha-blockers improve the outcomes of patients with stones stuck in their ureter?

Background

Stones stuck in the ureter, which is the tube that transports urine from the kidney to the bladder, often cause pain and make people see a doctor. Depending on which part of the ureter the stone is stuck in and the size of the stone, it will often pass into the bladder on its own over the course of weeks. If the stone does not come out by itself, people often need to have procedures done to remove the stone.

Alpha-blockers are medications that relax muscles in the urinary tract and may make the stone pass into the bladder faster. However, they can cause unwanted effects. We updated an existing Cochrane Review from 2014 to look into the effects of alpha-blockers.

Study characteristics

Based on our latest search of the literature from November 2017, we included 64 studies with 10,509 participants. Of these, 15 studies compared alpha-blockers with placebo with 5787 participants. A placebo is a pill that looks and tastes exactly like the real medication, so participants did not know what they were getting. These were the higher-quality studies, which we trusted more.

Key results

Based on the subset of higher-quality studies that used a placebo, alpha-blockers likely resulted in more people passing their stones. However, these patients are likely to experience slightly more serious unwanted effects of this medication.

People taking alpha-blockers may pass their stones in a shorter time, may use less diclofenac (which is a type of pain medication), and are likely to be admitted to the hospital less often. Meanwhile, the need for surgery for their stones was similar.

Upon completing additional analyses, we found that effects of alpha-blockers may be different in people with small (5 mm or smaller) versus larger (larger than 5 mm) stones. It appears that this medication works better in people with larger stones. We could find no difference in how well alpha-blockers work, no matter where in the ureter the stone is stuck or what type of alpha-blocker is used.

Authors' conclusions

For patients with stones stuck in the ureter, alpha-blockers likely make passing the stone easier but cause slightly more unwanted effects. It appears that alpha-blockers work better in people with larger (greater than 5 mm) rather than smaller (5 mm or smaller) stones.

Quality of the evidence

The quality of the evidence for most outcomes was moderate or low, meaning that we have moderate or low confidence in most of the reported results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Alpha-blockers compared with standard therapy for ureteral stones

Alpha-blockers compared with standard therapy for ureteral stones

Patient or population: adult patients presenting with symptoms of ureteral stone disease

Setting: single or multicenter

Intervention: alpha-blocker

Comparison: standard therapy

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard therapy	Risk difference with alpha-blockers
Stone clearance	10509 (67 RCTs)	⊕⊕⊕⊕ LOW ^{a,b,c}	RR 1.45 (1.36 to 1.55)	Study population 619 per 1000	 278 more per 1000 (223 more to 340 more)
Major adverse events	3124 (18 RCTs)	⊕⊕⊕⊕ LOW ^{a,d}	RR 1.25 (0.80 to 1.96)	Study population 20 per 1000	 5 more per 1000 (4 fewer to 19 more)
Stone expulsion time	6031 (37 RCTs)	⊕⊕⊕⊕ LOW ^{a,c,e}	-		MD 3.4 lower (4.17 lower to 2.63 lower)
Pain episodes	1363 (15 RCTs)	⊕⊕⊕⊕ LOW ^{a,c,f}	-		MD 0.66 lower (0.91 lower to 0.42 lower)
Dose of diclofenac	4373 (14 RCTs)	⊕⊕⊕⊕ LOW ^{a,c,g}	-		MD 82.41 mg lower (122.51 lower to 42.31 lower)
Hospitalisation	1876 (13 RCTs)	⊕⊕⊕⊕ MODERATE ^a	RR 0.51 (0.34 to 0.77)	Study population 141 per 1000	 69 fewer per 1000 (93 fewer to 32 fewer)

Surgical interven- tion	3292 (19 RCTs)	⊕⊕⊕⊕ LOW ^{a,d}	RR 0.74 (0.53 to 1.02)	Study population	
				109 per 1000	28 fewer per 1000 (51 fewer to 2 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aMost studies were rated as having high or unclear risk of bias.

^bClinically important heterogeneity with I² of 76%; provided rationale for downgrading together with suspected publication bias.

^cPublication bias suspected given funnel plot asymmetry.

^dConfidence interval consistent; no effect and clinically important harm.

^eClinically important heterogeneity with I² of 94%; provided rationale for downgrading together with suspected publication bias.

^fClinically important heterogeneity with I² of 80%; provided rationale for downgrading together with suspected publication bias.

^gClinically important heterogeneity with I² of 100%; provided rationale for downgrading together with suspected publication bias.

Summary of findings 2. Alpha-blockers compared with placebo for ureteral stones

Alpha-blockers compared with placebo for ureteral stones

Patient or population: adult patients presenting with symptoms of ureteral stone disease

Setting: single or multicenter

Intervention: alpha-blocker

Comparison: placebo

Outcomes	No. of partici- pants (studies) Follow-up	Quality of the evi- dence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with alpha-blockers
Stone clearance	5787	⊕⊕⊕⊕	RR 1.16	Study population	

	(15 RCTs)	MODERATE ^a	(1.07 to 1.25)	728 per 1000	116 more per 1000 (51 more to 182 more)
Major adverse events	1650 (10 RCTs)	⊕⊕⊕⊖ MODERATE ^b	RR 2.09 (1.13 to 3.86)	Study population 26 per 1000	29 more per 1000 (3 more to 75 more)
Stone expulsion time	3240 (7 RCTs)	⊕⊕⊕⊖ LOW ^{c,d}	-		MD 1.98 lower (3.71 lower to 0.24 lower)
Pain episodes	215 (2 RCTs)	⊕⊕⊕⊖ LOW ^{c,e}	-		MD 0.39 lower (1.07 lower to 0.29 higher)
Dose of diclofenac (mg)	3576 (4 RCTs)	⊕⊕⊕⊖ LOW ^{d,f}	-		MD 126.32 lower (181.73 lower to 70.9 lower)
Hospitalisation	500 (2 RCTs)	⊕⊕⊕⊖ MODERATE ^e	RR 0.84 (0.48 to 1.47)	Study population 96 per 1000	15 fewer per 1000 (50 fewer to 45 more)
Surgical intervention	1458 (5 RCTs)	⊕⊕⊕⊕ HIGH	RR 0.93 (0.70 to 1.24)	Study population 127 per 1000	9 fewer per 1000 (38 fewer to 30 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded owing to inconsistency (high heterogeneity with I² of 68%).

^bDowngraded owing to imprecision (wide confidence interval consistent with negligible to substantial harm).

^cDowngraded owing to inconsistency (heterogeneity with I² of 57%).

^dDowngraded owing to imprecision (wide confidence interval; wide confidence interval consistent with large to negligible benefit).

^eDowngraded owing to imprecision (wide confidence interval consistent with no effect and small benefit).

^fDowngraded owing to inconsistency (high heterogeneity with I^2 of 90%).

BACKGROUND

Description of the condition

Urinary stone disease refers to the formation of stones or calculi in the urinary tract and is one of the most common reasons for patients to visit a urology practice; it affects about 5% to 10% of the population (Ramello 2000). An even higher frequency of up to 12% has been reported from other parts of the world, and stone disease is rare in only a few geographical areas (e.g. Greenland, coastal areas of Japan) (Tiselius 2003). One study showed an increase in lifetime prevalence of stone disease ranging from 7.14% to 11.62% over a 10-year period (2000-2010) (Turney 2011). The incidence and prevalence rates of kidney stones may be affected by genetic, nutritional, and environmental factors. Caucasian males are more likely than Asians, Hispanics, and African Americans to develop urinary stones (Pearle 2007). Besides the probability of stone formation, stone composition and location in the urinary tract may differ among countries (Ramello 2000). Furthermore, in the USA, over 2 million outpatient visits for a primary diagnosis of urinary stones were recorded in 2000 (UDA 2012). Hospital outpatient visits increased by 40% between 1994 and 2000, and physician office visits increased by 43% between 1992 and 2000. Also in the USA, the total estimated annual cost for stone disease was over US \$10.3 billion in 2006 - showing an almost five-fold increase in six years (US \$2.1 billion in 2000) and representing a 50% increase since 1994. A further increase in costs to over US \$3 billion for emergency department visits was seen in the USA in 2009 (Ghani 2014). This rise could be explained only in part by the increasing prevalence of stone disease (Pearle 2005).

The natural history of urinary stone disease is characterised by specific steps - from formation of Randall's plaques to development of stones that cause renal or ureteral colic (Matlaga 2007). Symptoms include flank or abdominal pain radiating to the groin or external genitalia. Although some patients with ureteral stones might remain asymptomatic, many have pain and generally seek medical care. An acute episode of colic is the result of a stone entering the ureter and causing an intermittent rise in pressure in the pyelocalyceal system. Spontaneous passage does occur with most of these stones. Stone size and location are the two most important predictors of stone passage (Miller 1999). Passage rates of 68% for stones smaller than 5 mm and 47% for stones greater than 5 mm and up to 10 mm have been reported (Preminger 2007).

Current treatment modalities for ureteral stones include extracorporeal shockwave lithotripsy (ESWL); (flexible or semi-rigid) ureteroscopy; percutaneous nephrolithotomy; open surgery, laparoscopic surgery, or robot-assisted surgery; and observation with analgesia with or without adjuvant medications to facilitate stone passage (AUA Guideline 2016 Surgical Management of Stones; EAU guidelines on diagnosis and conservative management of urolithiasis 2016).

According to the guidelines of the European Association of Urology (EAU; EAU guidelines on diagnosis and conservative management of urolithiasis 2016) and the American Urologic Association (AUA; AUA Guideline 2016 Surgical Management of Stones), among patients with a newly diagnosed ureteral stone 10 mm or smaller whose symptoms are controlled, observation with periodic evaluation is an option for initial treatment. These patients may be offered an appropriate medical expulsive therapy to facilitate stone passage during the observation period. However, patients

should be informed about the attendant risks of medical expulsive therapy (including associated drug side effects) and should be told that these agents are administered for an 'off-label' use (Preminger 2007).

Description of the intervention

Different modalities of medical expulsive therapy have been evaluated, including alpha-blockers, calcium channel blockers, corticosteroids, and combinations of these. However, most experience has been acquired with alpha-blockers (Hollingsworth 2006; Michel 2006; Singh 2007).

How the intervention might work

Both α - and β -adrenergic receptors are present in the human ureter, although α -receptors predominate. More specifically, α_1 -receptors are important in lower ureteric physiology, and higher densities of α_1 -receptors have been discovered in the lower ureters of animals and humans (Nakada 2008). In the ureter, α_1 -receptor antagonists inhibit basal tone and decrease peristaltic frequency and amplitude. Consequently, intraureteral pressure might decrease and fluid transport might increase according to some study authors (Morita 1987). These receptors appear to be ideal targets for pharmacotherapy, as they represent the greatest impediment to stone passage (Sterrett 2008). Several trials in the past have assessed effects of alpha-blockers; most have reported favourable effects on stone clearance. We summarised this information in our previous review (Campschroer 2014).

Why it is important to do this review

Given the high rates of spontaneous passage ureteral stones, a study of medical expulsive therapy is warranted. Effective medical expulsive therapy confers several potential benefits. First, it may decrease the duration of symptoms of ureteral stones and, therefore, the rate of complications such as urinary tract infection (UTI), hydronephrosis, and kidney function impairment. Second, it can potentially decrease the use of more invasive interventions, such as ESWL and ureteroscopy, and therefore may decrease the rate of possible complications associated with these procedures. Last, medical expulsive therapy is likely to spare limited healthcare resources, such as physician time and hospital beds.

Despite the joint Guideline provided by the EAU and the AUA, considerable controversy persists concerning the best treatment approach for ureteral stones and the effectiveness of alpha-blocker use as medical expulsive therapy. Several published randomised controlled trials (RCTs) on this topic have presented conflicting conclusions. We have prepared an up-to-date systematic review of all available data from recent RCTs using the highest methodological standards and have applied the GRADE approach to rate the quality of evidence.

In summary, combining the studies performed so far provides the opportunity to produce an overall effect estimate of alpha-blockers as medical expulsive therapy for ureteral stones. The direction and magnitude of this effect can be used to guide decisions about clinical practice.

This current Cochrane Review presents an update of the previous Cochrane Review (Campschroer 2014). Since the last search was conducted (9 July 2012), several new studies have been published, making an update of this Cochrane Review necessary.

OBJECTIVES

To assess effects of alpha-blockers compared with standard therapy for ureteral stones 1 cm or smaller confirmed by imaging in adult patients presenting with symptoms of ureteral stone disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs and quasi-RCTs (trials in which investigators allocated participants to treatment using alternation, alternate medical records, date of birth, or other predictable methods) undertaken to investigate alpha-blockers for the treatment of adult patients with ureteral stones. We included eligible studies regardless of their publication status or language of publication.

Types of participants

Inclusion criteria

- Adult patients (aged 18 years or older)
- Symptoms of ureteral stones including flank or abdominal pain, possibly radiating to the groin or external genitalia
- Diagnosis confirmed upon imaging (e.g. plain film of the kidney, ureter, and bladder (KUB); computed tomography (CT); intravenous pyelography (IVP); ultrasonography (US))
- Single stone measuring 10 mm or smaller

Exclusion criteria

- Evidence of UTI or hydronephrosis with complicated factors (e.g. sepsis, uncontrollable pain, deterioration of renal function)
- Kidney or ureteral abnormalities (e.g. single kidney, ureteral malformation)
- Pregnant or lactating women
- Bilateral stones
- Taking an alpha-blocker or a calcium channel blocker, or having allergies to these medications

Types of interventions

Interventions include medical expulsive therapy with alpha-blockers to treat patients with ureteral stones versus one of two comparators: (1) standard therapy (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antispasmodics), or (2) placebo. When one study assessed multiple alpha-blockers, we combined arms for the comparison of alpha-blockers versus standard therapy or placebo. We conducted subgroup analyses to explore whether effects differ among various alpha-blockers.

We excluded studies in which researchers evaluated alpha-blockers as an adjuvant to surgery or lithotripsy. If patients used other medication such as anticholinergics or antispasmodics as an adjuvant to trial medication, we evaluated only comparable groups (e.g. patients in a standard therapy group using anticholinergics vs patients in the trial group using anticholinergics combined with trial medication).

Types of outcome measures

Primary outcomes

- Stone clearance (dichotomous outcome defined as percentage of participants identified as stone-free by diagnostic imaging on the last day of the study trial, or participants who were symptom-free at the end of the trial, or participants who had expelled their stone and brought it with them to the follow-up visit)
- Major adverse events (dichotomous outcome defined as the number of participants who experienced orthostatic hypotension, collapse, syncope, palpitations, or tachycardia)

Secondary outcomes

- Stone expulsion time (continuous outcome defined as days from start of inclusion until stone expulsion)
- Pain episodes (continuous outcome defined as number of pain episodes)
- Diclofenac use (continuous outcome defined as cumulative dosage of diclofenac in milligrams)
- Hospitalisation (dichotomous outcome defined as percentage of participants needing hospital admission because of uncontrollable pain or complicating factors such as UTI or sepsis)
- Surgical intervention (dichotomous outcome defined as the number of participants who require surgical intervention as the result of uncontrolled pain and/or hydronephrosis within the trial period)

Main outcomes for 'Summary of findings' tables

We present 'Summary of findings' tables to report the following outcomes listed according to priority.

Comparison 1 (Analysis 1): alpha-blockers versus standard therapy or placebo ([Summary of findings for the main comparison](#)).

- 1.1 Stone clearance.
- 1.2 Major adverse events.
- 1.3 Stone expulsion time.
- 1.4 Pain episodes.
- 1.5 Dose of diclofenac [mg].
- 1.6 Hospitalisation.
- 1.7 Surgical intervention.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group Specialized Register for the first version of this Cochrane Review through contact with the Trial Search Co-ordinator using search terms relevant to this review (search date 9 July 2012). TC and XZ updated the search on 18 November 2017, by using the following sources.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017 November 18) in the Cochrane Library.
- MEDLINE (via Ovid 1946 to 18 November 2017).

- MEDLINE In-Process & Other Non-Indexed Citations (18 November 2017).
- Embase (via Ovid 1980 to 18 November 2017).
- PubMed (inception to November 2017) (18 November 2017).
- International Clinical Trials Registry Platform (ICTRP) search portal ([WHO ICTRP](#)) and [ClinicalTrials.gov](#) (18 November 2017).
- Proceedings of major (mainly renal and stone disease) conferences from 2005 to November 2017: EAU (European Association of Urology); AUA (American Urological Association); ESD (Experts in Stone Disease); WCE (World Congress of Endourology); and SIU (Société Internationale d'Urologie).

We imposed no restrictions, for example, on language or publication status for the searches described above.

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

- Reference lists of urology textbooks, review articles, and relevant studies. Furthermore, review authors scrutinised the reference lists of identified relevant studies for additional citations.
- Letters sent to request information about unpublished or incomplete studies to investigators known to be involved in previous studies.

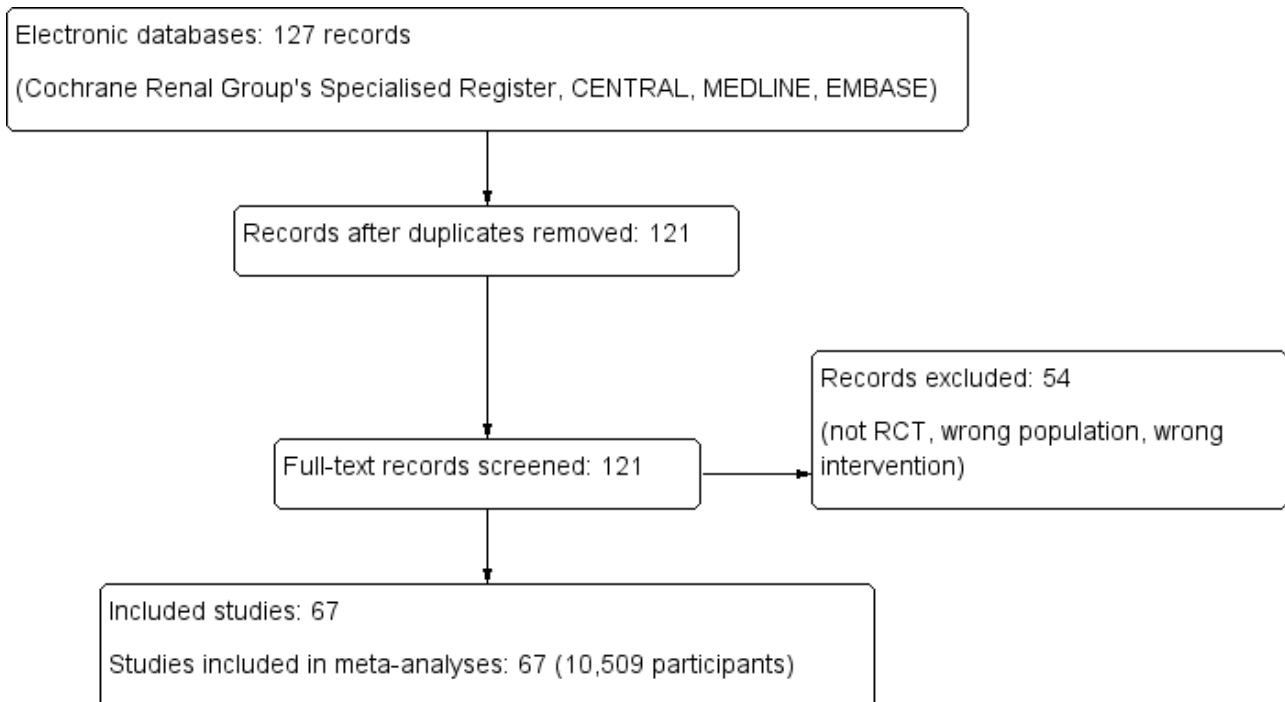
Data collection and analysis

Selection of studies

We used reference management software to identify and remove duplicate records ([Endnote 2016](#)). Two review authors (TC and XZ) independently assessed the titles and abstract of records identified in the search against the predefined inclusion criteria to determine which studies should be assessed in the full-text evaluation. The same review authors (TC and XZ) investigated all records included in the title/abstract screening as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved discrepancies through discussion or arbitration by a third review author (TL). If resolution of a disagreement was not possible, we designated the study as 'Awaiting classification' and contacted the study authors for clarification. We documented in [Characteristics of excluded studies](#) tables reasons for exclusion of studies that may have reasonably been expected to be included in the review.

We summarised in [Characteristics of included studies](#) tables relevant study characteristics, including sample size, gender of participants, stone size, and stone location. We have shown the flow of literature through the assessment process in a PRISMA flowchart ([Figure 1](#)).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (TC and XZ) independently carried out data extraction using standard data extraction forms. We tested the forms before implementation in the review. We translated studies reported in non-English language journals before assessment. In the case that more than one publication of the same

study existed, we grouped reports together and included the publication with the most complete data. If outcome data were available at multiple time points during follow-up of one trial, we extracted solely outcomes with the longest follow-up. We highlighted any discrepancies between published versions. We resolved disagreements by consulting with another review author

(TL). For dichotomous outcomes, we extracted the number of participants with the specific outcome and the denominator of the total participants for whom the outcome was assessed at longest follow-up. For continuous outcomes, we extracted the number of participants for whom the outcome was measured and determined the mean value and standard deviation (SD) for each outcome. We requested through written correspondence any further information required from the original author(s) and included in the review any relevant information obtained in this manner. When original trial author(s) did not respond to this correspondence, we excluded that study from the review.

Assessment of risk of bias in included studies

Review authors (TC and XZ) independently assessed the risk of bias of each included study. We resolved disagreements by consensus or by consultation with a third review author (TL).

Using the Cochrane 'Risk of bias' assessment tool ([Higgins 2011](#)), we assessed risk of bias using the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We have presented 'Risk of bias' summary figures to illustrate these findings ([Figure 2](#) and [Figure 3](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdel-Meguid 2010	+	+	+	?	?	+	+
Agrawal 2009	?	?	?	?	+	+	+
Ahmad 2015	?	?	?	?	+	+	+
Ahmed 2010	?	?	?	?	?	+	+
Al Ansari 2010	+	+	+	+	?	+	+
Albert 2016	?	?	?	?	+	-	+
Aldemir 2011	?	?	?	?	+	-	+
Alizadeh 2014	?	?	?	?	?	-	+
Arrabal-Martin 2010	?	?	?	?	+	+	+
Autorino 2005	+	?	?	?	+	+	+
Ayubov 2007	?	?	?	?	?	+	?
Bajwa 2013	+	?	?	?	+	-	+
Balci 2014	+	?	?	?	+	?	+
Bayraktar 2017	-	?	?	+	+	+	-
Berger 2015	-	?	+	?	-	+	+
Cervenakov 2002	?	?	?	?	+	+	+
Cha 2012	+	+	?	?	+	+	+
Cho 2017	+	+	+	?	+	+	+
Doluoglu 2015	+	+	?	+	-	-	+
Dong 2009	-	?	?	?	?	?	?

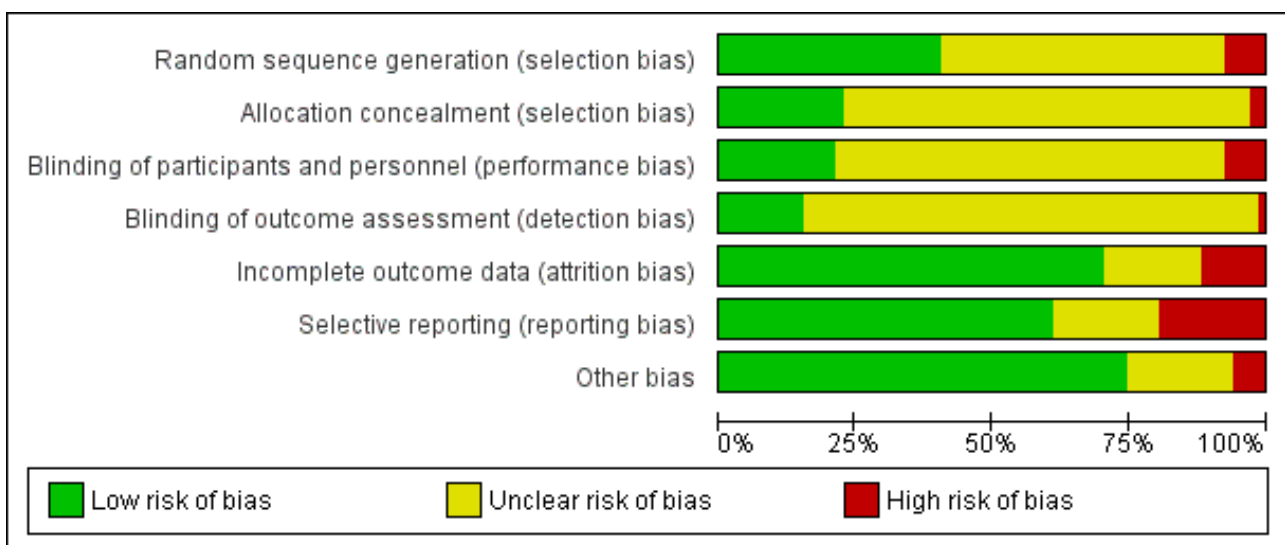
Figure 2. (Continued)

Dong 2009	+	?	?	?	?	?	?
El-Gamal 2012	+	+	+	?	+	-	+
El Said 2015	+	?	-	-	+	+	+
Erkan 2011	?	?	?	?	-	?	?
Erturhan 2007	?	?	?	?	+	+	+
Eryildirim 2015	+	?	?	?	?	+	+
Ferre 2009	+	+	?	?	+	+	+
Furyk 2016	+	+	+	+	+	+	+
Georgescu 2015	+	+	?	?	+	+	+
Griwan 2010	?	?	?	?	+	-	+
Han 2006a	?	?	?	?	?	?	?
Hermanns 2009	+	+	+	+	+	+	+
Hong 2008	?	?	?	?	-	+	?
Ibrahim 2013	?	?	?	?	-	?	+
Islam 2010	?	?	?	?	+	-	+
Itoh 2011	?	?	?	?	?	-	?
Itoh 2013	+	?	?	?	+	+	-
Kaneko 2010	+	?	?	?	+	+	+
Kim 2007b	?	?	?	?	?	?	?
Kupeli 2004	+	?	?	+	+	+	+
Lee 2014	+	?	-	?	-	+	+
Liatsikos 2007	-	-	-	?	+	-	+
Lojanapiwat 2008	?	?	-	?	+	+	+
Lojanapiwat 2012	?	?	?	?	?	?	?
Maitra 2012	?	?	?	?	+	-	-
Meltzer 2017	?	?	+	?	+	?	?
Mshemish 2012	?	?	?	?	-	?	-
Mukhtarov 2007	?	?	?	?	+	?	?
Ochoa-Gomez 2011	?	?	+	?	+	+	+
Park 2012	?	?	?	?	-	+	?
Pedro 2008	+	+	+	?	+	+	+

Figure 2. (Continued)

Pedro 2008	+	+	+	?	+	+	+
Pickard 2015	+	+	+	+	+	+	?
Porpiglia 2006	?	?	?	?	+	+	+
Porpiglia 2009	?	?	?	?	+	+	+
Rahim 2012	+	?	?	?	+	-	+
Sayed 2008	?	?	?	?	+	+	+
Sen 2017	+	?	?	?	+	?	+
Sun 2009	?	?	?	?	+	-	+
Sur 2015	+	+	+	+	+	+	+
Taghavi 2005	?	?	?	?	?	?	?
Vincendeau 2010	+	+	+	+	+	+	+
Wang 2008a	+	?	?	?	+	+	+
Ye 2017	+	+	+	+	+	+	+
Yencilek 2010	?	?	?	?	+	+	+
Yilmaz 2005	?	?	?	?	+	+	+
Yuksel 2015	?	?	?	?	+	?	+
Zehri 2010	-	-	-	?	+	+	+
Zhou 2011	?	?	?	?	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and we grouped outcomes according to whether they were measured subjectively or objectively when reporting our findings in the 'Risk of bias' tables.

We also assessed attrition bias (incomplete outcome data) on an outcome-specific basis and grouped outcomes with like judgements when reporting our findings in the 'Risk of bias' tables.

We further summarised risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

For assessment of performance bias, we judged all outcomes to be equally susceptible to bias.

For assessment of detection bias, we defined the following endpoints as susceptible to bias (subjective).

- Stone clearance.
- Major adverse events.
- Stone expulsion time.
- Pain episodes.

For assessment of detection bias, we defined the following endpoints as not susceptible to bias (objective).

- Dose of diclofenac.
- Hospitalisation.
- Surgical intervention.

We assessed risk of bias of included studies using the bias assessment tool provided by [Higgins 2011](#) (see [Appendix 2](#)).

Measures of treatment effect

We analysed all data using Review Manager version 5.3.

For dichotomous outcomes (stone clearance, major adverse events, hospitalisation, surgical intervention), we expressed results as risk ratios (RRs) with 95% confidence intervals (CIs). When we used continuous scales of measurement to assess effects of treatment (stone expulsion time, pain episodes, dose of diclofenac), we used mean differences (MDs) with 95% CIs if the same scales were used.

Unit of analysis issues

The unit of analysis is the study. In studies that included more than two intervention groups (e.g. tamsulosin and alfuzosin, different dosages of the same alpha-blocker), we collapsed the separate treatment arms into one for our main analysis. If intervention groups could not be separated, or if it was unclear whether studies from the same author with a trial period in the same year had overlapping participants, we asked trial authors to provide us the exact data separately. When we received no reaction or a denial on our request, we had to exclude the study.

Dealing with missing data

We did not impute any data, and we did not have sufficient information to perform an intention-to-treat analysis for all trials. We took this into account when we assessed risk of bias.

We requested by written or electronic correspondence any further information or clarification required from trial authors, and we included in the review relevant data obtained in this manner.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of forest plots to assess the extent of overlap of CIs, and we used the I^2 statistic to quantify inconsistency across studies to assess the impact of heterogeneity on the meta-analysis ([Higgins 2002](#); [Higgins 2003](#)). We interpreted I^2 as follows.

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

Assessment of reporting biases

We attempted to obtain study protocols to assess studies for selective outcome reporting. If we included 10 or more studies investigating a particular outcome, we used funnel plots to assess small-study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We therefore interpreted results with caution ([Sterne 2001](#)).

Data synthesis

For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method; and for time-to-event outcomes, we used the generic inverse variance method. We used Review Manager software to perform analyses ([Review Manager 2014](#)).

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses to explore possible sources of heterogeneity (e.g. participants, interventions).

- Stone size (stones measuring 5 mm or smaller vs stones measuring 6 to 10 mm).
- Stone location (distal ureter stones vs mid or proximal ureter stones).
- Type of alpha-blocker.

We used this rationale in performing the subgroup analyses mentioned above because previous studies suggested possible subgroup effects ([Campschroer 2014](#); [Hollingsworth 2016](#); [Preminger 2007](#)).

We limited outcomes for subgroup analyses to data available from the included studies (i.e. analyses were performed only when stratification according to our subgroups was provided).

Sensitivity analysis

We conducted the following sensitivity analyses to explore possible sources of heterogeneity in study design.

- Solely placebo-controlled trials, excluding trials with standard therapy as the control group.
- Solely high-quality trials, excluding trials with high risk of bias.

'Summary of findings' tables and application of GRADE

We presented the overall quality of evidence for each outcome according to the GRADE approach, which takes into account five criteria related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity (e.g. directness of results) (Guyatt 2008). Two review authors (TC and XZ) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low', and resolved discrepancies by consensus, or, if needed, by arbitration provided by a third review author (TL). We presented a summary of the evidence for main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of overall confidence in effect estimates for each outcome (Guyatt 2008; Schünemann 2006).

RESULTS

Description of studies

Results of the search

Initially, we found 127 records through database searching and identified no additional records through other sources. On the basis of our criteria, we identified 121 potentially relevant titles and retrieved the full text of these articles for further evaluation (Figure 1).

Included studies

Finally, we included 67 studies in this review (Characteristics of included studies).

Most studies (52 of 67) compared a standard therapy group versus an alpha-blocker group. Standard therapy consisted of appropriate hydration and use of NSAIDs, corticosteroids, or antispasmodics. Fifteen of the 67 studies compared alpha-blocker versus placebo. Ten of the 67 studies were carried out in a multi-centre setting (Cho 2017; Dong 2009; Furyk 2016; Lee 2014; Lojanapiwat 2008; Meltzer 2017; Pickard 2015; Sur 2015; Vincendeau 2010; Ye 2017). Sample size varied from 30 to 3450 and mean or median age from 32 to 56 years, and the duration of follow-up ranged from one week to eight weeks.

Some studies had multiple intervention arms (Agrawal 2009; Ahmed 2010; Albert 2016; Aldemir 2011; Balci 2014; Cha 2012; Dong 2009; El-Gamal 2012; Erkan 2011; Erturhan 2007; Georgescu 2015; Hong 2008; Ibrahim 2013; Islam 2010; Kupeli 2004; Liatsikos 2007; Lojanapiwat 2008; Maitra 2012; Mshemish 2012; Mukhtarov 2007; Pickard 2015; Porpiglia 2006; Sen 2017; Taghavi 2005; Wang 2008a; Yilmaz 2005; Zhou 2011). Ten studies compared different alpha-blockers, such as tamsulosin (0.4 mg), alfuzosin (10 mg), doxazosin (4 or 8 mg), terazosin (2 or 5 mg), naftopidil (10 mg), or silodosin (8 mg), with each other and with a standard therapy or placebo (Agrawal 2009; Ahmed 2010; Albert 2016; Cha 2012; Georgescu 2015; Ibrahim 2013; Mshemish 2012; Wang 2008a; Yilmaz 2005; Zhou 2011). Lojanapiwat 2008 and Cha 2012 used different dosages of tamsulosin (0.2 and 0.4 mg). Six studies used tamsulosin 0.2

mg (Cha 2012; Dong 2009; Han 2006a; Kaneko 2010; Kim 2007b; Lojanapiwat 2008).

Excluded studies

We excluded 54 studies (Characteristics of excluded studies).

Investigators in four studies gave participants calcium channel blockers, not alpha-blockers (Borghi 1994; Cooper 2000; Porpiglia 2000; Skrekas 2003). Five studies treated participants with invasive treatment modalities (ureteral stent positioning, ESWL, or ureterorenoscopy with lithotripsy) (Agrawal 2009; Damiano 2008; Deliveliotis 2006; John 2010; Wang 2009c). We excluded eight studies because they included participants with ureteral stones larger than 10 mm, or with multiple stones (Aravintan 2012; Avdoshin 2005; Dellabella 2003; Dellabella 2005; Gandhi 2013; Khawaja 2005; Mohseni 2006; Resim 2005). We could not compare study groups from 14 studies for this review, or investigators used no standard therapy/placebo (Cuni 2013; Dellabella 2005a; Gupta 2013; Gupta Shyam 2014; Gurbuz 2011; Imperatore 2014; Jayant 2014; Kumar 2014; Kumar 2015; Lu 2012; Morozumi 2013; Salem 2015; Shabana 2015; Tsuzaka 2011). We excluded nine studies because of study design (no RCTs) (Brausi 2015; Hwang 2012; Itano 2012; Loftus 2015; Moon 2015; Multescu 2014; Nasim 2014; Reddy 2016; Resorlu 2011; Shah 2013; Tchev 2011; Tsuzaka 2011; Vavassori 2012). Other reasons for exclusion were enrolment of children (Aydogdu 2009; Sameer 2014), insufficient recruitment (ISRCTN24675122), addition of corticosteroid drugs to tamsulosin (Dellabella 2005a), inclusion of patients with pyelonephritis (Chau 2011), and insufficient primary and secondary outcome data or data that could not be interpreted (Bak 2007; Bhat 2015; Haxhiu 2014; Ohgaki 2010; Ramesh 2015; Su 2016; Sumer 2012).

Risk of bias in included studies

See Figure 2 and Figure 3.

Allocation

Of the 67 studies, 36 and 50 studies described methods of sequence generation and allocation, respectively, with unclear risk of selection bias. Twenty-six and 15 studies had low risk of bias, respectively. We judged five and two studies as having high risk of bias, respectively.

Blinding

In total, we judged 48 and 56 studies as having unclear risk of performance and detection bias, respectively. Fourteen and 10 studies had low risk of bias, respectively. We judged five studies and one study as having high risk of bias, respectively.

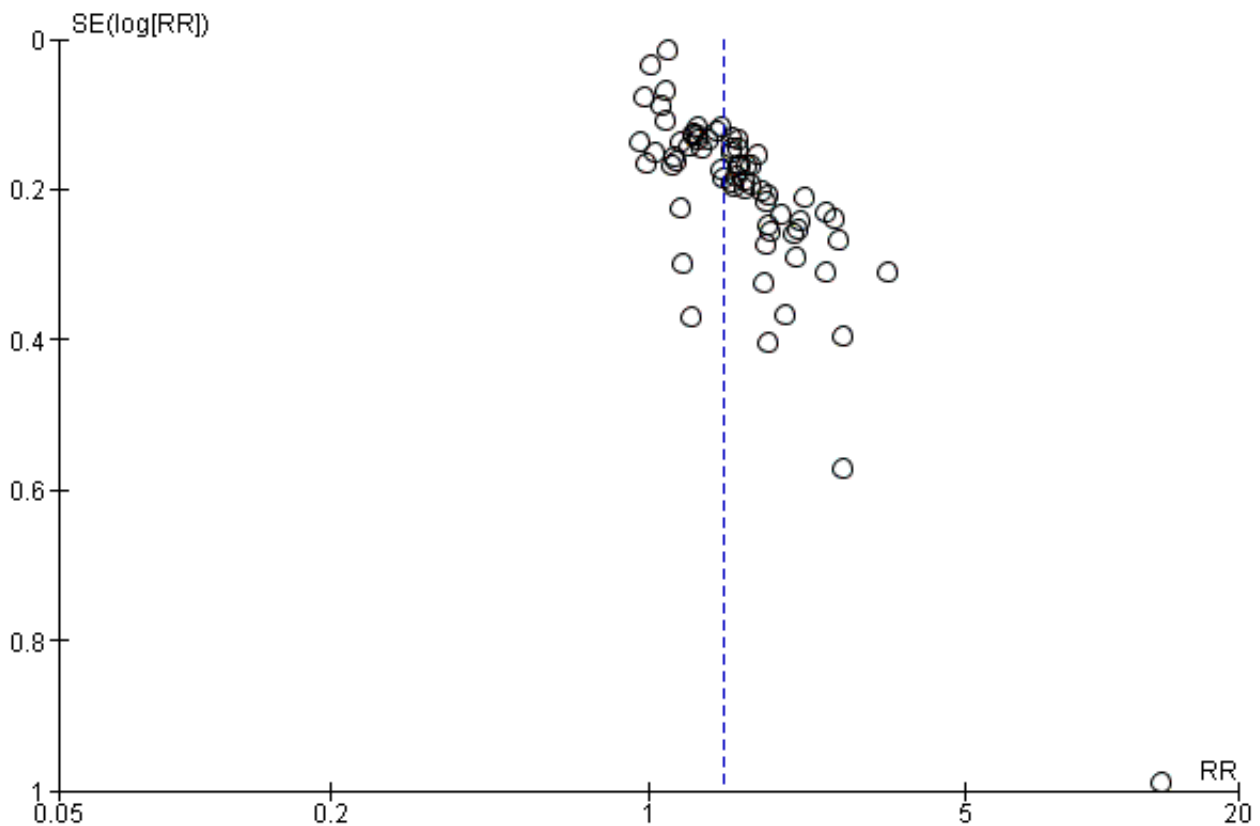
Incomplete outcome data

In total, we judged 47 studies as having low risk of attrition bias. Twelve studies had unclear risk of bias. Eight studies had high risk of bias.

Selective reporting

The funnel plot as shown in Figure 4 was asymmetrical. Of the 67 included studies, we judged 42 as having low risk of reporting bias. Twelve studies had unclear risk of bias. Thirteen studies had high risk of bias.

Figure 4. Funnel plot of comparison: 1 Alpha-blocker versus standard therapy or placebo, outcome: 1.1 Stone clearance.



Other potential sources of bias

In total, we considered 50 studies as having low risk of other potential sources of bias. Thirteen studies had unclear risk of bias. We judged four studies as having high risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Alpha-blockers compared with standard therapy for ureteral stones](#); [Summary of findings 2 Alpha-blockers compared with placebo for ureteral stones](#)

1. Alpha-blockers versus standard therapy or placebo

See [Summary of findings for the main comparison](#) and [Summary of findings 2](#).

Primary outcomes

1.1 Stone clearance

A total of 67 RCTs with 10,509 participants showed that treatment with an alpha-blocker may result in a large increase in stone clearance ([Analysis 1.1](#); RR 1.45, 95% CI 1.36 to 1.55; $P < 0.00001$; $I^2 = 76\%$; low-quality evidence); this corresponds to 278 more (95% CI 223 more to 340 more) stone clearances per 1000. We downgraded the quality of evidence for study limitations, inconsistency, and concerns about publication bias.

1.2 Major adverse events

Eighteen studies with 3124 participants described major adverse events. Treatment with an alpha-blocker may have little effect on major adverse events ([Analysis 1.2](#); RR 1.25, 95% CI 0.80 to 1.96; $P = 0.33$; $I^2 = 0\%$; low-quality evidence); this corresponds to 5 more (95% CI 4 fewer to 19 more) major adverse events per 1000. We downgraded the quality of evidence for study limitations and imprecision.

Seven studies reported discontinuation of treatment due to adverse events ([Hermanns 2009](#); [Itoh 2011](#); [Itoh 2013](#); [Pedro 2008](#); [Sen 2017](#); [Sur 2015](#); [Vincendeau 2010](#)). In some studies, discontinuation of treatment due to adverse events was unclear ([Meltzer 2017](#); [Pickard 2015](#)).

In total, 59 major adverse events occurred in 3124 participants receiving alpha-blockers, and 28 major adverse events were reported in 1329 participants receiving standard therapy or placebo.

Eleven of 1735 participants (0.6%) in the alpha-blocker group discontinued treatment within the study because of major adverse events, as compared with 1 of 1389 (0.07%) in the control group.

Secondary outcomes

1.3 Stone expulsion time

A total of 37 studies with 6031 participants described stone expulsion time. Treatment with an alpha blocker may substantially reduce the time to stone passage ([Analysis 1.3](#); MD -3.40 days, 95% CI -4.17 to -2.63; $P < 0.00001$; $I^2 = 94%$; low-quality evidence). We downgraded the quality of evidence for study limitations, inconsistency, and concerns about publication bias.

1.4 Pain episodes

A total of 15 studies with 1363 participants reported the number of pain episodes. Treatment with an alpha-blocker may provide a small reduction in the number of pain episodes ([Analysis 1.4](#); MD -0.66, 95% CI -0.91 to -0.42; $P < 0.00001$; $I^2 = 80%$; low-quality evidence). We downgraded the quality of evidence for study limitations, inconsistency, and concerns about publication bias.

1.5 Dose of diclofenac

On the basis of 14 studies with 4373 participants, we are uncertain whether treatment with an alpha-blocker reduces the use of diclofenac ([Analysis 1.5](#); MD -82.41, 95% CI -122.51 to -42.31; $P < 0.00001$; $I^2 = 100%$; low-quality evidence). It is notable that the dose of diclofenac in the standard therapy group varied largely among studies (from 15 mg to 1405 mg). We downgraded the quality of evidence for study limitations, inconsistency, and concerns about publication bias.

1.6 Hospitalisation

Findings of 13 studies with 1876 participants show that treatment with an alpha-blocker may reduce the need for hospitalisation ([Analysis 1.6](#); RR 0.51, 95% CI 0.34 to 0.77; $P = 0.001$; $I^2 = 40%$; moderate-quality evidence). This corresponds to 69 fewer (95% CI 93 fewer to 32 fewer) hospitalisations per 1000. We downgraded the quality of evidence for study limitations.

1.7 Surgical intervention

A total of 19 studies with 3292 participants reported that treatment with an alpha-blocker may have little effect on the need for surgical intervention ([Analysis 1.7](#); RR 0.74, 95% CI 0.53 to 1.02; $P = 0.07$; $I^2 = 37%$; low-quality evidence). This corresponds to 28 fewer (95% CI 51 fewer to 2 more) surgical interventions per 1000. We downgraded the quality of evidence for study limitations and imprecision.

Subgroup analyses

Stone size

2.1 Stone clearance

We compared outcomes of participants with stones measuring 5 mm or smaller (14 studies, 2622 participants) versus outcomes of those with stones bigger than 5 mm (10 studies, 2887 participants; [Analysis 2.1](#)). We found an RR of 1.06 (95% CI 0.98 to 1.15; $P = 0.16$; $I^2 = 62%$) versus 1.45 (95% CI 1.22 to 1.72; $P < 0.0001$; $I^2 = 59%$), respectively. The test for interaction was suggestive of a possible subgroup effect ($\text{Chi}^2 = 9.96$, $P = 0.002$; $I^2 = 90%$). Therefore, alpha-blockers may have little effect on stone clearance in participants with stones measuring 5 mm or smaller, resulting in 48 more (95% CI 16 fewer to 121 more) stone clearances per 1000, but may substantially increase stone clearance in participants with stones bigger than 5 mm, which corresponds to 302 more (95% CI 148 more to 483 more) stone clearances per 1000. We rated the quality of

evidence as moderate upon downgrading for study limitations and imprecision.

2.2 Stone expulsion time

Stratified by stone size, participants with stones measuring 5 mm or smaller did benefit from using alpha-blockers compared with standard therapy or placebo in terms of stone expulsion time ([Analysis 2.2](#); six studies, 1264 participants) (MD -1.07, 95% CI -1.99 to -0.15; $P = 0.02$; $I^2 = 60%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision. For stones bigger than 5 mm, the alpha-blocker group had shorter stone expulsion time ([Analysis 2.2](#); four studies, 1884 participants) (MD -5.99, 95% CI -7.16 to -4.82; $P < 0.00001$; $I^2 = 77%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision.

The subgroup interaction test did not indicate a difference in effect for stone expulsion time based on stone size ($\text{Chi}^2 = 41.91$, $P < 0.00001$; $I^2 = 97.6%$).

2.3 Other outcomes

We found no studies that reported the outcomes of major adverse events, pain episodes, dose of diclofenac, hospitalisation, and surgical intervention that permitted an analysis stratified by stone size.

Stone location

3.1 Stone clearance

For participants with distal ureteral stones, stone clearance may be improved ([Analysis 3.1](#); 57 studies, 8576 participants) (RR 1.46, 95% CI 1.36 to 1.57; $P < 0.00001$; $I^2 = 77%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and publication bias.

For participants with mid and proximal ureteral stones, stone clearance was similar ([Analysis 3.1](#); nine studies, 794 participants) (RR 1.28, 95% CI 0.99 to 1.66; $P = 0.06$; $I^2 = 60%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision.

Tests for subgroup differences were not statistically significant ($\text{Chi}^2 = 0.93$, $I^2 = 0%$, $P = 0.34$).

3.2 Stone expulsion time

Participants with distal ureteral stones may benefit from using alpha-blockers compared with standard therapy or placebo in terms of stone expulsion time ([Analysis 3.2](#); 32 studies, 5453 participants) (MD -3.43, 95% CI -4.26 to -2.60; $P < 0.0001$; $I^2 = 95%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision. For mid or proximal ureteral stones, the alpha-blocker group did not show shorter stone expulsion time ([Analysis 3.2](#); two studies, 146 participants) (MD -8.64, 95% CI -19.75 to 2.48; $P = 0.13$; $I^2 = 96%$). The quality of evidence was moderate upon downgrading for risk of bias and imprecision.

The subgroup interaction test indicated a difference in effect for stone expulsion time based on stone location ($\text{Chi}^2 = 0.84$, $P = 0.36$, $I^2 = 0%$).

3.3 Other outcomes

We found no studies that reported the outcomes of major adverse events, pain episodes, dose of diclofenac, hospitalisation, and surgical intervention that permitted an analysis stratified by stone location.

Type of alpha-blocker

4.1 Stone clearance

We performed a subgroup analysis based on types of alpha-blockers used; these included tamsulosin, alfuzosin, terazosin, naftopidil, and silodosin ([Analysis 4.1](#)). All types of alpha-blockers improved stone clearance. The subgroup test for interaction did not show significance ($\text{Chi}^2 = 1.44$, $I^2 = 0\%$, $P = 0.92$).

4.2 Major adverse events

We performed a subgroup analysis based on types of alpha-blockers used; these included tamsulosin, alfuzosin, doxazosin, terazosin, naftopidil, and silodosin ([Analysis 4.2](#)). Major adverse events were not increased, except with alfuzosin (five studies, 323 participants) (RR 5.51, 95% CI 1.46 to 20.83; $P = 0.01$; $I^2 = 0\%$). However, the subgroup test for interaction did not show significance ($\text{Chi}^2 = 5.57$, $I^2 = 46.1\%$, $P = 0.13$).

4.3 Stone expulsion time

We performed a subgroup analysis based on types of alpha-blockers used; these included tamsulosin, alfuzosin, terazosin, naftopidil, and silodosin ([Analysis 4.3](#)). Use of an alpha-blocker consistently shortened time to stone passage. The subgroup test for interaction did not show significance ($\text{Chi}^2 = 23.76$, $I^2 = 79.0\%$, $P = 0.0002$).

4.4 Pain episodes

We performed a subgroup analysis based on types of alpha-blockers used; these included tamsulosin, alfuzosin, doxazosin, terazosin, naftopidil, and silodosin ([Analysis 4.4](#)). Pain episodes were consistently decreased, except with silodosin (two studies, 150 participants) (MD -0.89, 95% CI -2.05 to 0.26; $P = 0.13$; $I^2 = 80\%$). The subgroup test for interaction did not show significance ($\text{Chi}^2 = 3.02$, $I^2 = 0\%$, $P = 0.70$).

4.5 Dose of diclofenac (mg)

We performed a subgroup analysis based on types of alpha-blockers used; these included tamsulosin, doxazosin, terazosin, and silodosin ([Analysis 4.5](#)). Diclofenac use was consistently decreased. The subgroup test for interaction did not show significance ($\text{Chi}^2 = 1.37$, $I^2 = 0\%$, $P = 0.71$).

4.6 Hospitalisation

Tamsulosin versus standard therapy or placebo showed fewer hospitalisations in favour of alpha-blockers ([Analysis 4.6](#); 11 studies, 1606 participants) (RR 0.57, 95% CI 0.38 to 0.86; $P = 0.007$; $I^2 = 33\%$). The risk difference for participants receiving tamsulosin was 58 fewer more (95% CI 19 fewer to 84 fewer) hospitalisations per 1000. The quality of evidence was moderate upon downgrading for risk of bias.

Alfuzosin did not show a beneficial effect in the alpha-blocker group in terms of hospitalisation ([Analysis 4.6](#); two studies, 110 participants) (RR 0.35, 95% CI 0.09 to 1.45; $P = 0.15$; $I^2 = 0\%$). The risk difference for participants receiving alfuzosin was 84 fewer

(95% CI 118 fewer to 58 more) hospitalisations per 1000. The quality of evidence was low upon downgrading for risk of bias and imprecision.

Use of doxazosin did not result in fewer hospitalisations ([Analysis 4.6](#); two studies, 132 participants) (RR 0.19, 95% CI 0.01 to 3.05; $P = 0.24$; $I^2 = 78\%$). The risk difference for participants receiving doxazosin was 282 fewer (95% CI 345 fewer to 714 more) hospitalisations per 1000. The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision.

Silodosin versus standard therapy or placebo showed fewer hospitalisations in the alpha-blocker group ([Analysis 4.6](#); two studies, 180 participants) (RR 0.26, 95% CI 0.12 to 0.55; $P = 0.0005$; $I^2 = 0\%$). The risk difference for participants receiving silodosin was 222 fewer (95% CI 135 fewer to 264 fewer) hospitalisations per 1000. The quality of evidence was moderate upon downgrading for risk of bias.

Testing for subgroup differences was not statistically significant ($\text{Chi}^2 = 3.77$, $I^2 = 20.4\%$, $P = 0.29$).

4.7 Surgical intervention

Use of tamsulosin did not lead to fewer surgical interventions ([Analysis 4.7](#); 16 studies, 2820 participants) (RR 0.82, 95% CI 0.59 to 1.13; $P = 0.22$; $I^2 = 29\%$). The risk difference for participants receiving tamsulosin was 21 fewer (95% CI 49 fewer to 15 more) surgical interventions per 1000. The quality of evidence was moderate upon downgrading for risk of bias.

Alfuzosin did not result in less surgical interventions ([Analysis 4.7](#); one study, 58 participants) (RR 0.47, 95% CI 0.09 to 2.35, $P = 0.36$). The risk difference for participants receiving alfuzosin was 76 fewer (95% CI 130 fewer to 193 more) surgical interventions per 1000. The quality of evidence was low upon downgrading for risk of bias and imprecision.

Use of doxazosin did not result in fewer surgical interventions ([Analysis 4.7](#); two studies, 133 participants) (RR 0.41, 95% CI 0.15 to 1.11; $P = 0.08$; $I^2 = 0\%$). The risk difference for participants receiving doxazosin was 89 fewer (95% CI 128 fewer to 17 more) surgical interventions per 1000. The quality of evidence was low upon downgrading for risk of bias and imprecision.

Data show no difference in terms of surgical interventions between silodosin versus standard therapy or placebo ([Analysis 4.7](#); three studies, 133 participants) (RR 0.41, 95% CI 0.15 to 1.11; $P = 0.11$; $I^2 = 27\%$). The risk difference for participants receiving silodosin was 25 fewer (95% CI 33 fewer to 11 more) surgical interventions per 1000. The quality of evidence was low upon downgrading for risk of bias and imprecision.

Testing for subgroup differences did not show statistical significance ($\text{Chi}^2 = 3.52$, $I^2 = 14.9\%$, $P = 0.32$).

Sensitivity analyses

Alpha-blockers versus placebo

5.1 Stone clearance

Participants who received alpha-blockers were more likely to be stone-free compared with those who received placebo ([Analysis 5.1](#); 15 studies, 5787 participants) (RR 1.16, 95% CI 1.07 to 1.25, $P < 0.00001$; $I^2 = 68\%$). The risk difference with alpha-blockers was 116

more (95% CI 51 more to 182 more) stone clearances per 1000. The quality of evidence was moderate upon downgrading for risk of bias and inconsistency.

5.2 Major adverse events

Participants using alpha-blockers experienced more major adverse events of the medication compared with those given placebo ([Analysis 5.2](#); 10 studies, 1650 participants) (RR 2.09, 95% CI 1.13 to 3.86; $P = 0.02$; $I^2 = 25\%$). The risk difference with alpha-blockers was 29 more (95% CI 3 more to 75 more) major adverse events per 1000. The quality of evidence was moderate upon downgrading for risk of bias and imprecision. For 4 of the 848 (0.47%) participants in the alpha-blocker group, the major adverse event led to cessation of therapy versus none in the placebo group.

5.3 Stone expulsion time

Stone expulsion time was shorter among participants using alpha-blockers compared with those receiving placebo ([Analysis 5.3](#); seven studies, 3240 participants) (MD -1.98, 95% CI -3.71 to -0.24; $P = 0.03$; $I^2 = 76\%$). The quality of evidence was low upon downgrading for inconsistency and imprecision.

5.4 Pain episodes

The number of pain episodes was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 5.4](#); two studies, 215 participants) (MD -0.39, 95% CI -1.07 to 0.29; $P = 0.13$; $I^2 = 57\%$). The quality of evidence was low upon downgrading for inconsistency and imprecision.

5.5 Dose of diclofenac (mg)

The dose of diclofenac used was statistically lower for participants using alpha-blockers compared with those receiving placebo ([Analysis 5.5](#); four studies, 3576 participants) (MD -126.32, 95% CI -181.73 to -70.90; $P < 0.00001$; $I^2 = 90\%$). The quality of evidence was low upon downgrading for risk of bias, inconsistency, and imprecision.

5.6 Hospitalisation

Hospitalisation was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 5.6](#); two studies, 500 participants) (RR 0.84, 95% CI 0.48 to 1.47; $P = 0.55$; $I^2 = 0\%$). The risk difference with alpha-blockers was 15 fewer (95% CI 50 fewer to 45 more) hospitalisations per 1000. The quality of evidence was moderate upon downgrading for risk of bias and imprecision.

5.7 Surgical intervention

Surgical intervention was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 5.7](#); five studies, 1458 participants) (RR 0.93, 95% CI 0.70 to 1.24; $P = 0.39$; $I^2 = 1\%$). The risk difference with alpha-blockers was 9 fewer (95% CI 38 fewer to 30 more) surgical interventions per 1000. The quality of evidence was high.

High-quality studies

6.1 Stone clearance

Data show statistically significant higher stone clearance between intervention and control groups in the high-quality sensitivity analysis ([Analysis 6.1](#); five studies, 4133 participants) (RR 1.09, 95% CI 1.06 to 1.13; $P < 0.00001$; $I^2 = 0\%$). The risk difference with alpha-

blockers was 68 more (95% CI 45 more to 98 more) stone clearances per 1000. The quality of evidence was high.

6.2 Major adverse events

Participants using alpha-blockers did not experience more major adverse events of the medication compared with those given placebo ([Analysis 6.2](#); two studies, 515 participants) (RR 0.94, 95% CI 0.51 to 1.72; $P = 0.84$; $I^2 = 0\%$). The risk difference with alpha-blockers was 5 fewer (95% CI 38 fewer to 56 more) major adverse events per 1000. The quality of evidence was moderate upon downgrading for imprecision.

6.3 Stone expulsion time

Stone expulsion time was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 6.3](#); three studies, 2891 participants) (MD -1.72, 95% CI -5.13 to 1.68; $P = 0.32$; $I^2 = 86\%$). The quality of evidence was low upon downgrading for inconsistency and imprecision.

6.4 Pain episodes

The number of pain episodes was not statistically different between participants using alpha-blockers and those given placebo ([Analysis 6.4](#); one study, 119 participants) (MD 0.00, 95% CI -0.72 to 0.72; $P = 1$). The quality of evidence was moderate upon downgrading for imprecision.

6.5 Dose of diclofenac (mg)

The dose of diclofenac used was statistically lower among participants using alpha-blockers compared with those receiving placebo ([Analysis 6.5](#); two studies, 3386 participants) (MD -173.28, 95% CI -277.60 to -68.95; $P = 0.001$). The quality of evidence was moderate upon downgrading for imprecision.

6.6 Hospitalisation

Hospitalisation was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 6.6](#); one study, 403 participants) (RR 0.87, 95% CI 0.49 to 1.52; $P = 0.62$). The risk difference with alpha-blockers was 15 fewer (95% CI 58 fewer to 60 more) hospitalisations per 1000. The quality of evidence was moderate upon downgrading for imprecision.

6.7 Surgical intervention

Surgical intervention was not statistically different between participants using alpha-blockers and those receiving placebo ([Analysis 6.7](#); three studies, 605 participants) (RR 0.94, 95% CI 0.38 to 2.32; $P = 0.90$; $I^2 = 34\%$). The risk difference with alpha-blockers was 3 fewer (95% CI 33 fewer to 70 more) surgical interventions per 1000. The quality of evidence was moderate upon downgrading for imprecision.

DISCUSSION

Summary of main results

The main findings of this meta-analysis are that greater stone clearance can be achieved with medical expulsive therapy with an alpha-blocker than with standard therapy without an alpha-blocker (low-quality evidence). Use of alpha-blockers does not appear to result in an increase in major adverse events (low-quality evidence).

Based on a preplanned sensitivity analysis of placebo-controlled studies only, we found alpha-blockers to be less effective than was suggested by the overall analysis of all studies; this finding corresponds to greater stone clearance (moderate-quality evidence) and an increase in major adverse events (moderate-quality evidence).

By performing a preplanned subgroup analysis, we found support for a possible subgroup effect based on stone size; alpha-blockers may provide clinically meaningful improvement in stone clearance among patients with stones measuring 6 to 10 mm, but not among patients with stones measuring 5 mm or less. We did not find evidence of a subgroup effect based on stone location or type of alpha-blocker.

For secondary outcomes, treatment with alpha-blockers appears to shorten the time to stone expulsion and reduce the number of pain episodes, use of diclofenac, and the need for hospitalisation (very low- to moderate-quality evidence). Our subgroup analyses showed a possible subgroup effect of stone size based on testing for interaction suggesting a larger effect in stones measuring 6 to 10 mm in size. For stone location and type of alpha-blocker, the test for subgroup differences did not show statistical significance.

Overall completeness and applicability of evidence

For this review, we performed an extensive search: Two of three review authors independently extracted and managed trial data and resolved disagreements in consultation with the third review author. To collect additional potentially useful journal articles, we had non-English language journals translated, and we asked authors of studies with missing data to deliver these data by written correspondence.

We assessed risk of bias using Cochrane's 'Risk of bias' assessment tool and assessed the quality of evidence (see below) through the GRADE approach. It should be noted that on the basis of funnel plot asymmetry, we suspected publication bias for several outcomes, which led to downgrading of evidence quality.

Follow-up involved radiological examination in 50 of 67 studies (74.6%). Four studies (6.3%) did not perform radiological

assessment, and in 13 (20.3%) studies, it was unclear whether this was done. We believe that radiological confirmation is warranted to assess stone clearance, although review of images by (especially not-blinded) radiologists may have introduced bias.

Because studies were conducted in a wide variety of countries worldwide over several continents (i.e. North America, Europe, and Asia), the results of this review are probably applicable worldwide.

Furthermore, we want to point out the potential issue of incomplete reporting of major adverse events.

Quality of the evidence

We used GRADE to assess the quality of evidence on a per-outcome basis and frequently lowered the quality of evidence. The main issues that lowered our confidence in estimates of effect were study limitations, specifically unclear allocation concealment, lack of blinding resulting in performance and detection bias, and potential attrition bias.

Other issues that prompted frequent downgrading were clinically important inconsistency in study results, imprecision, and concerns over potential publication bias in the light of observed funnel plot asymmetry.

Last, most studies did not prospectively stratify for clinically important subgroups at the time of randomisation; therefore it is unclear whether prognostic balance existed. Therefore, the results of these secondary analyses must be interpreted with caution.

Potential biases in the review process

We searched with no language restrictions. However, despite our best efforts, which included contacting the principal investigators of existing studies, we may have missed some studies that were published in non-indexed journals or were not published.

We investigated reporting bias using funnel plots, which showed asymmetry for stone clearance and major adverse events ([Figure 4](#); [Figure 5](#); [Figure 6](#)). We performed sensitivity analyses after excluding non-placebo-controlled trials and still found a favourable effect of alpha-blockers on stone clearance when we suspected publication bias.

Figure 5. Funnel plot of comparison: 1 Alpha-blocker versus standard therapy or placebo, outcome: 1.2 Major adverse events.

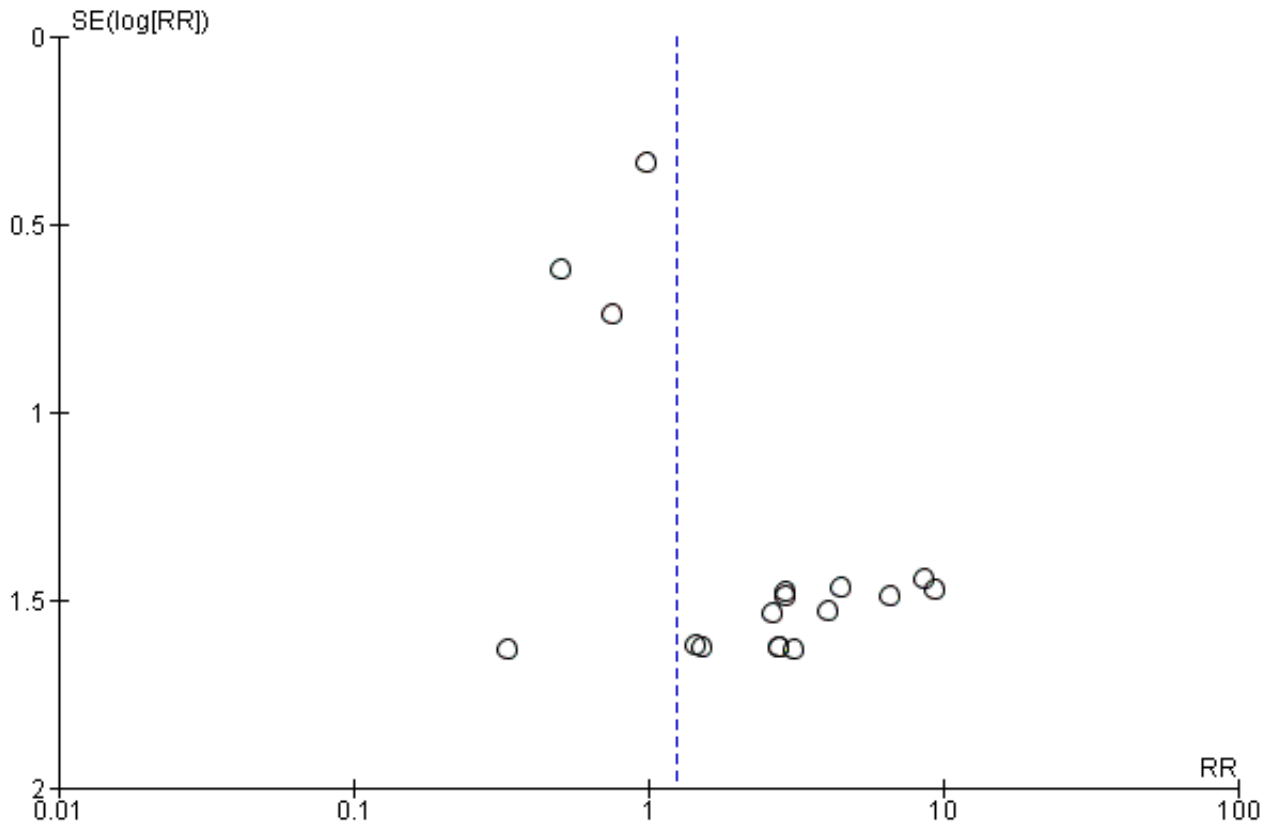
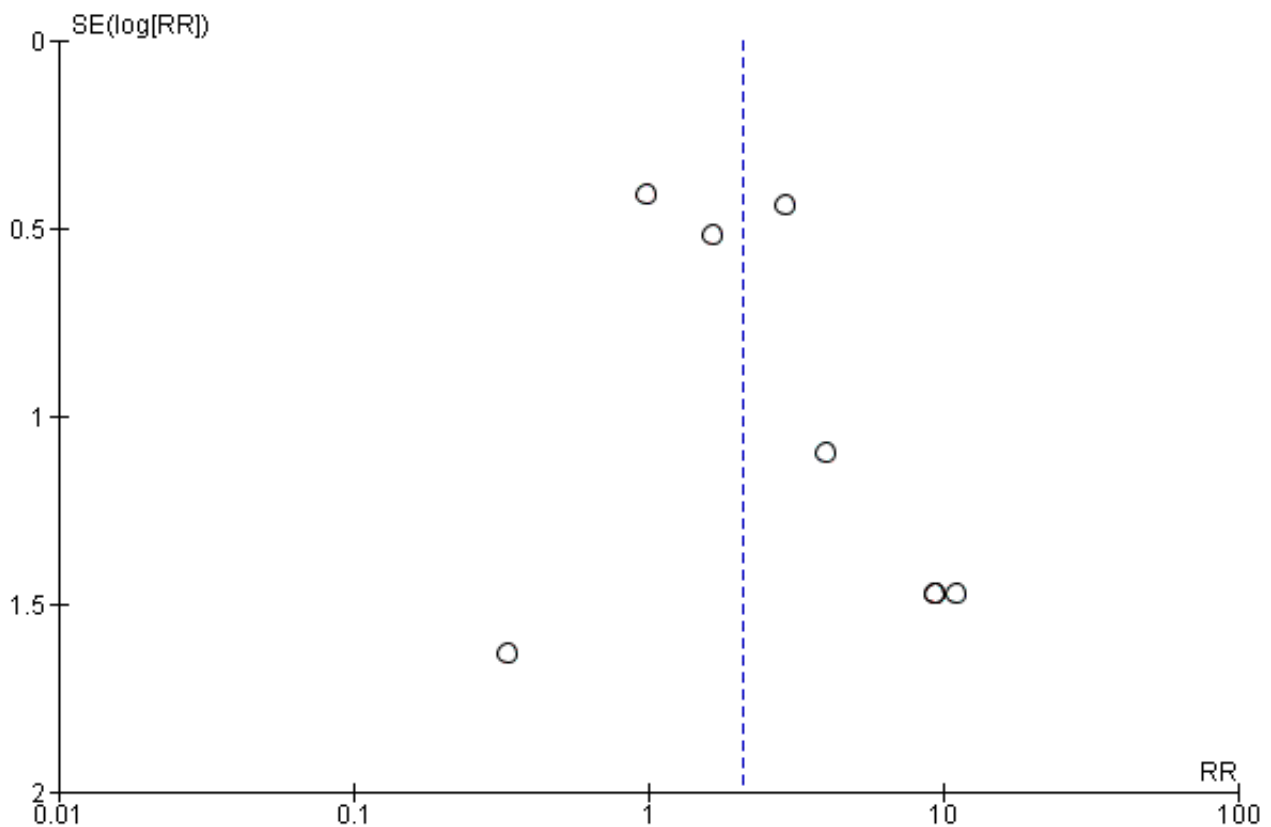


Figure 6. Funnel plot of comparison 2: Alpha-blocker versus placebo, outcome: 2.2 Major adverse events.



Agreements and disagreements with other studies or reviews

Although many systematic reviews have examined this topic, very few have been conducted with the same methodological rigour that is standard for Cochrane Reviews. This review is the most up-to-date and includes the unpublished and relatively large study that was presented by Meltzer and colleagues at AUA 2017 (Meltzer 2017).

Most earlier trials examining alpha-blockers for ureteral stones conclude that stone clearance and stone expulsion time are improved. From 2013 to 2015, multiple meta-analyses were performed for different alpha-blockers (tamsulosin, silodosin, and alfuzosin; Fan 2013; Huang 2015; Liu 2015, respectively) and those results were similar to findings discussed in the present review. In a meta-analysis performed in 2016 by Hollingsworth and colleagues (Hollingsworth 2016), review authors came to similar principal findings as ours, stating that alpha-blockers should be considered for use in individuals with ureteral stones. The Hollingsworth meta-analysis included some multi-centre placebo-controlled randomised controlled trials (RCTs) that did not demonstrate beneficial effects of alpha-blockers on stone clearance when compared with placebo (Furyk 2016; Pickard 2015; Sur 2015). We included these studies in the current meta-analysis as well. Two of these trials involved a large percentage of individuals with small stones (75% of patients taking alpha-blockers had stones measuring 5 mm or smaller) (Furyk 2016; Pickard 2015). However, because smaller stones are more likely to pass spontaneously (even without medical expulsive therapy),

this fact could have influenced the overall effect noted in these studies (i.e. the potential benefits of medical expulsive therapy may have been diluted by the inclusion of smaller stones in these two studies). Closer analysis of the data of Furyk and colleagues reveals a favourable effect in the tamsulosin group versus the placebo group for stones measuring 5 to 10 mm. The present review endorses this finding, as included trials reported significant effects of alpha-blockers in individuals with larger stones (6 mm or bigger) in terms of stone clearance and possible differences in effect detected by subgroup interaction testing.

The SUSPEND trial by Pickard and colleagues was designed to assess the clinical effectiveness of medical expulsive therapy rather than therapeutic efficacy, as radiological assessment was not a primary endpoint (Pickard 2015). Although these trial authors concluded that medical expulsive therapy is not effective in reducing the need for intervention at four weeks, differences in stone clearance were attenuated for stones larger than 5 mm, favouring tamsulosin as compared with nifedipine and placebo (71.3%, 61.7%, and 60.6%, respectively). Moreover, the response rate for both 4-week (62%) and 12-week questionnaires (49%) was considerably lower than that noted in primary outcome participation but could influence secondary outcome results. Investigators in the SUSPEND trial did not monitor medication adherence, and this could raise some concerns. Results of the SUSPEND trial may have led to changes in clinical practice in some countries. However, this is not consistent with findings derived from our meta-analysis, which demonstrated a persistent beneficial effect of alpha-blockers for distal ureteral stones larger than 5 mm.

Consistent with the SUSPEND trial, data show no difference in surgical interventions between groups. In line with findings of the SUSPEND trial, a very small proportion of participants receiving alpha-blockers experienced major adverse events, and even a smaller proportion discontinued treatment because of this.

Sur and colleagues found a positive effect of alpha-blockers for individuals with distal ureteral stones upon performing a subgroup analysis (Sur 2015). This is in line with the findings of the present review (i.e. that the greatest effect of alpha-blockers can be effectuated in the distal part of the ureter and can be achieved in patients with stones measuring 6 to 10 mm).

More recently, an abstract was presented at AUA 2017 that reported on a trial included in our meta-analysis (Meltzer 2017). These trial authors also failed to demonstrate a favourable effect of alpha-blockers. However, investigators assessed stone clearance through telephone calls and by participant reporting. About 50% of participants underwent follow-up computed tomography (CT), revealing no difference in stone clearance between groups. In this trial, about 75% of participants had stones smaller than 5 mm; no results from any subgroup analyses based on stone size are available for this unpublished study. Apart from abnormalities of ejaculation, treatment-related adverse events did not occur more often in the alpha-blocker group.

The most recently published paper describes favourable effects of tamsulosin reported by Ye and colleagues for the largest trial yet (Ye 2017). This double-blind, placebo-controlled study, which included distal stones, demonstrated specific benefit of tamsulosin for larger stones (> 5 mm), although trial authors reported no results from testing for interaction. Data show no differences in the incidence of adverse events between the two study groups, and investigators reported no serious adverse events. These findings are supported by a unique feature of this study, in that participants underwent weekly non-contrast computed tomography scans.

AUTHORS' CONCLUSIONS

Implications for practice

Results of both the main analysis and a predefined subgroup analysis of placebo-controlled studies indicate that alpha-blockers improve stone clearance but may slightly increase the risk of major adverse events. Use of alpha-blockers may also improve several other patient-important outcomes. This information should provide valuable guidance to clinicians, patients, and guideline developers for decision-making about the use of alpha-blockers.

For clinical settings in which stone size is known, evidence from this review suggests that the effectiveness of alpha-blockers is most often proportionate to stone size. Patients with larger stones (>5mm) will benefit most from an alpha-blocker, because smaller stones often tend to pass spontaneously even without the use of an alpha-blocker. This may have important implications for consideration of selective use of alpha-blockers if, for example, stone size has been determined accurately by imaging. Meanwhile, we based on the test of interaction, we cannot confirm that stone clearance differs by stone location. Furthermore, we found no evidence that the effectiveness of alpha-blockers on investigated outcomes differs by the type of alpha-blocker used.

Implications for research

Whereas most trials on medical expulsive therapy with alpha-blockers were of low methodological quality, prompting us to downgrade analyses for study limitations, we have identified a subset of higher-quality, placebo-controlled studies. Through this approach, we found evidence of at least moderate quality for the outcome stone clearance. For these outcomes, future trials appear unlikely to change our understanding of the effects of alpha-blockers and may not be needed.

Data show less certainty with regards to other outcomes. Moderate quality of evidence was found for the primary outcome major adverse events with conflicting results when selecting placebo-controlled studies only (more adverse events in alpha-blocker group) or high-quality studies only (no difference in adverse events between both groups). Results on stone expulsion time, the need for pain medication, hospitalisation and need for surgical intervention are secondary outcomes with low to moderate quality of evidence. These outcomes should be investigated in future trials to further explore the effectiveness of alpha-blockers on these parameters. In addition, some uncertainty surrounds the relative effectiveness of alpha-blockers in terms of stone location. Future studies should be placebo-controlled and should implement adequate allocation concealment, blinding of all relevant parties (participants, personnel, and outcome assessors), and complete or near-complete follow-up. In addition, studies should be stratified and adequately powered for any planned secondary analyses such as those related to stone size and location.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdel-Meguid 2010

Methods	<ul style="list-style-type: none"> Study design: parallel RCT. Study duration: June 2008 to December 2009. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Saudi Arabia. Setting: single centre. Adults > 18 years of either sex; single, unilateral, newly diagnosed condition; 4-10 mm in transverse diameter; distal ureteral stones; normal kidney function. Number: treatment group 75; control group 75. Median age (range, years): treatment group 34 (20-67); control group 36 (19-72). Sex, M/F: treatment group: 50/25; control group: 53/22. Exclusion criteria: history of ipsilateral ureteral endoscopic or surgical manipulations or ESWL; patients with symptomatic UTI; those pregnant or lactating; patients already receiving alpha-blockers, beta-blockers, calcium channel antagonists, or corticosteroids; serious medical conditions; refused randomisation; lost to follow-up during the study period.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. Hydration, analgesia (diclofenac 100 mg) as needed. <p>Control group</p> <ul style="list-style-type: none"> Placebo. Hydration, analgesia (diclofenac 100 mg) as needed.
Outcomes	<ul style="list-style-type: none"> Stone passage rate. Stone passage time. Weekly stone passage rate. Episodes of renal colic. Need for analgesia. Drug adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Baseline assessment included non-contrast spiral CT and furthermore weekly follow-ups with KUB and US. NCCT was repeated at end of study to confirm stone status.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated randomly in 1:1 ratio into either group." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Using sealed envelopes."

Abdel-Meguid 2010 (Continued)

		Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both treating physicians and patients were blinded to randomization." Comment: double-blind and therefore low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessments described. Comment: No description was available; therefore this method of outcome assessment was considered to have unclear risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "17 patients were excluded due to not accepting randomization (6) and loss to follow-up during study period (4 in group A and 7 in group B)." Comment: Owing to relatively high numbers of exclusions and losses to follow-up, incomplete outcome data were stated and risk of bias was unclear.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias therefore was considered to be low.
Other bias	Low risk	No quotes available. The study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Agrawal 2009

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: September 2004 to August 2007. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: India. • Setting: single centre. • Patients with stone < 10 mm in size in the distal ureter; evaluated with KUB, US, intravenous urography, and NCCT in selected patients. • Number: treatment group 1: 34; treatment group 2: 34; control group: 34. • Median age (range, years): treatment group 1: 31.4 (15-56); treatment group 2: 38.7 (19-60); control group: 35.3 (22-58). • Sex, M/F: treatment group 1: 26/8; treatment group 2: 28/6; control group: 24/10. • Exclusion criteria: UTI; severe hydronephrosis; diabetes mellitus; multiple stones; hypotension; pregnancy; previous spontaneous stone expulsion; distal ureteral surgery; history of intake of warfarin/alpha-blocker/calcium channel blocker/steroids and cimetidine.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Alfuzosin 10 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Placebo.

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Agrawal 2009 (Continued)

All groups received 75 mg diclofenac intramuscularly and were advised to drink at least 3 L of fluids.

Outcomes	<ul style="list-style-type: none"> • Stone passage. • Time for passage. • Total diclofenac dosage. • Number of pain episodes.
Funding sources	None.
Declarations of interest	None.
Notes	Follow-up weekly with KUB and US.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized to 3 groups." Comment: Randomisation was stated, but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, risk of allocation concealment was considered to be unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Spontaneous stone expulsion was observed in 28 of 34 patients (82.3%) in group 1, 24 of 34 (70.5%) in group 2, and 12 of 34 (35.2%) patients in group 3." Comment: Stone expulsion rate was reported for all participants; therefore, probably none were lost to follow-up and accordingly risk of bias was considered low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. The study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Ahmad 2015

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: 1 January to 31 October 2010. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Pakistan. • Setting: single centre. • Patients with stone ≤ 8 mm in the distal 1/3 ureter; evaluated with KUB, US, or IVU (if required). • Number: treatment group: 49; placebo group: 48. • Mean age, SD, years: overall: 36.34; range: 18-57. • Sex, M/F: not reported. • Exclusion criteria: age < 18 years; ureteric obstruction; distal ureteric stricture; previous ureteral surgery; solitary kidney; aberrant ureteral anatomy (e.g. ureteral ectopia, ureterocoele, mega-ureter); UTI; radiolucent stone.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. <p>Placebo group</p> <ul style="list-style-type: none"> • Placebo. <p>Both groups were given tab diclofenac sodium 50 mg, 1 tab 8 hourly for pain control on required basis.</p>
Outcomes	<ul style="list-style-type: none"> • Stone passage rate. • Time for stone passage. • Need for analgesics. • Need for hospitalisation. • Drug adverse effects.
Funding sources	None.
Declarations of interest	None.
Notes	Participants were evaluated with plain X-ray KUB after 2 weeks and 4 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned into one of the two groups." Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, risk of allocation concealment was considered to be unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described.

Ahmad 2015 (Continued)

		Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients lost to follow up, therefore 97 out of 100 patients were evaluated." Comment: Small number of participants were lost to follow-up; accordingly, risk of bias was considered low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered low.

Ahmed 2010

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: March 2008 and November 2009. • Follow-up/Treatment duration: 30 days.
Participants	<ul style="list-style-type: none"> • Country: Saudi Arabia. • Setting: single centre. • Patients with stone ≤ 10 mm in the distal ureter; evaluated with KUB, US, and NCCT in selected patients. • Number: treatment group 1: 29; treatment group 2: 30; control group: 28. • Mean age, SD, years: treatment group 1: 40.7 ± 14.8; treatment group 2: 41.1 ± 15.2; control group: 38.9 ± 13.3. • Sex, M/F: treatment group 1: 19/10; treatment group 2: 18/12; control group: 19/9. • Exclusion criteria: age < 18 years; pregnant or lactating women; history of previous surgery on the ipsilateral ureter; stone larger than 10 mm; multiple stones; bilateral ureteric stones; solitary kidney; UTI; moderate or severe hydronephrosis; currently on alpha-blocker therapy; known allergy to tamsulosin or alfuzosin; contraindications to non-steroidal anti-inflammatory agents; renal insufficiency.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Alfuzosin 10 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac sodium only. <p>All groups received 50 mg diclofenac every 12 hours for 1 week, then 75 mg diclofenac intramuscularly as needed up to 2 times per day.</p>
Outcomes	<ul style="list-style-type: none"> • Stone passage rate. • Time for stone passage. • Frequency of pain attacks. • Complications of medications.

Ahmed 2010 (Continued)

Funding sources	None.
Declarations of interest	None.
Notes	Follow-up visits on a weekly basis with urine analysis, serum creatinine measurement, plain X-ray KUB, and abdominal ultrasonography. Abdominal CT was performed for participants with radiolucent stones if the stone was not expelled by the end of study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 90 patients with distal ureteral stones ≤ 10 mm in diameter were randomly divided into 3 equal groups and given medications for 30 days." Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. No intention-to-treat analysis. Comment: Owing to lack of intention-to-treat analysis, risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Al Ansari 2010

Methods	<ul style="list-style-type: none"> • Study design: double-blinded RCT. • Study duration: May 2007 to May 2009. • Follow-up: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Qatar. • Setting: single centre.

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Al Ansari 2010 (Continued)

- Patients with distal ureteral stones of 10 mm or smaller, evaluated by KUB, US, and NCCT before treatment.
- Number: treatment group: 50; control group: 50.
- Mean age \pm SD, years: treatment group: 37.18 \pm 9.38; control group: 36.13 \pm 9.32.
- Sex, M/F: treatment group: 32/18; control group: 29/21.
- Exclusion criteria: age < 18 years; non-radiopaque stones; multiple stones; severe hydronephrosis; pregnancy; hypotension; peptic ulcer; history of endoscopic or open ureteral surgery; use of calcium channel blocker.

Interventions	Treatment group <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. Control <ul style="list-style-type: none"> • Placebo.
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Time for stone passage. • Number of pain episodes. • Need for diclofenac injection. • Total diclofenac dosage. • Blood pressure. • Possible side effects.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Sample size calculated. Weekly follow-up with KUB, US, and urine analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized between study and placebo medications using a computer-generated random number assignment, adjusted at a ratio of 1:1." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization data were kept strictly confidential, in sealed envelopes, accessible only to the pharmacist at the end of the study." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigators and patients were masked to the type of the treatment throughout the study." Comment: double-blind; therefore low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigators and patients were masked to the type of the treatment throughout the study." Comment: Personnel responsible for outcome assessments were blinded; therefore risk of detection bias was considered to be low.

Al Ansari 2010 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Four patients in the placebo group were lost to follow-up." Comment: Four participants in the placebo group were lost to follow-up and were excluded from analysis. It is unclear whether this had a clinically relevant impact on the intervention effect estimate; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias therefore was considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered low.

Albert 2016

Methods	<ul style="list-style-type: none"> Study design: RCT. Study duration: December 2013 to June 2015. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: India. Setting: single centre. Patients with stone ≤ 10 mm in the distal ureter; evaluated with KUB, US, and NCCT in selected patients. Number: treatment group 1: 40; treatment group 2: 40; control group: 40. Mean age, SD, years: treatment group 1: 35 ± 8.5; treatment group 2: 32 ± 7.5; control group: 34 ± 8.5. Sex, M/F: treatment group 1: 28/12; treatment group 2: 32/8; control group: 30/10. Exclusion criteria: age < 18 years; previous surgery on ipsilateral ureter; bilateral ureteral calculus; multiple stones; solitary kidney; intolerant or hypersensitive to alpha-blockers; contraindicated for NSAIDs; renal insufficiency; pregnant and lactating women
Interventions	Treatment group 1 <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. Treatment group 2 <ul style="list-style-type: none"> Silodosin 8 mg once daily. Control group <ul style="list-style-type: none"> All groups received 50-100 mg diclofenac.
Outcomes	<ul style="list-style-type: none"> Stone passage rate. Blood pressure. Time for stone passage. Number of pain attacks. Hospital re-admissions. Adverse effects.
Funding sources	None.

Albert 2016 (Continued)

Declarations of interest	None.	
Notes	Follow-up visits on a weekly basis with urine analysis, serum creatinine measurement, plain X-ray KUB, and abdominal ultrasonography. Abdominal CT was performed for all participants by end of study.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quote available. Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Out of the 120 patients included in the study, patients were divided randomly into three groups of 40 patients." Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Blood pressure was not reported in the Results section (as a secondary outcome measurement); therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered low.

Aldemir 2011

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: March to July 2009. • Follow-up: 10 days.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Patients with distal ureteral stones < 10 mm; > 17 years; diagnosed with KUB, US, and CT if necessary. • Number: treatment group 1: 31; treatment group 2: 30; control group: 29.

Aldemir 2011 (Continued)

- Mean age \pm SD, years: treatment group 1: 42.4 \pm 16.1; treatment group 2: 46.5 \pm 16.5; control group: 43.5 \pm 16.6.
- Sex, M/F: treatment group 1: 22/9; treatment group 2: 17/13; control group: 19/10.
- Exclusion criteria: presence of UTI; solitary kidney; severe hydronephrosis; renal insufficiency; diabetes mellitus; multiple stones; bilateral stones; hypotension; pregnancy; previous spontaneous stone expulsion; previous distal ureteral surgery; history of intake of nifedipine, alpha-adrenergic blockers, calcium antagonists, and steroids

Interventions	Treatment group 1 <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. Treatment group 2 <ul style="list-style-type: none"> • Rowatinex 100 mg once daily. Control group <ul style="list-style-type: none"> • Diclofenac 100 mg once daily. Participants in groups 1 and 2 received diclofenac when needed (100 mg once daily).
Outcomes	<ul style="list-style-type: none"> • Mean stone expulsion time. • Stone expulsion rate. • Mean stone size. • Stone location. • Stone site. • Additional analgesic requirement. • Number of ureteral colics. • Upper urinary tract dilation. • Adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Missing data on stone expulsion rate. Follow-up was 10 days, then again KUB, US, or CT. All participants were suggested to drink at least 2 L of drinking water daily.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized in 3 groups." Comment: Randomisation was stated, but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias)	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.

Aldemir 2011 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: No predefined endpoints were mentioned; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered low.

Alizadeh 2014

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: June 2007 until July 2008. • Follow-up: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Iran. • Setting: single centre. • Patients with distal ureteral stones and UVJ stones 3 to 6 mm; 18-60 years; diagnosed with KUB and US. • Number: treatment group: 50; control group: 46. • Age limits, years: treatment group: 20-50; control group: 19-54. • Sex, M/F: treatment group: 21/29; control group: 14/32. • Exclusion criteria: radiolucent stone on KUB; acute hydronephrosis (grades 2 and 3) on sonography; presence of UTI; history of peptic ulcer disease; systolic blood pressure < 100; consumers of calcium antagonist drugs; solitary kidney; diabetes mellitus; pregnancy; previous distal ureteral surgery; creatinine over 1.4 for males and 1.2 for females; pain resistant to conservative treatment; NSAID intolerance or adverse events of tamsulosin during the study; participant withdrawal from the study at any time; occurrence of any unforeseen complications during the study.
Interventions	<p>Control group</p> <ul style="list-style-type: none"> • Standard pain medication (indomethacin). <p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. <p>Researchers emphasised that all participants should drink 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion time. • Stone expulsion rate. • Mean stone size. • Stone location. • Amount of analgesic consumption. • Possible complications caused by stones during the study period.

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Alizadeh 2014 (Continued)

- Possible side effects from medications or intolerance recorded and used for statistical analysis.

Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up was every 2 weeks with KUB, US, or CT. Not all abbreviations were explained in the text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned to a control group (n = 46) and study group (n = 50)." Comment: Randomisation was stated but no information on method used was available; therefore selection bias was considered to have unclear risk.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. No intention-to-treat analysis. Comment: Owing to lack of intention-to-treat analysis, risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Results on pain episodes were not reported; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore we considered risk of other bias to be low.

Arrabal-Martin 2010

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: December 2007 and November 2008. • Follow-up: 3 weeks.
Participants	<ul style="list-style-type: none"> • Country: Spain.

Arrabal-Martin 2010 (Continued)

- Setting: single centre.
- Patients with distal ureteral stones diagnosed with KUB, ultrasound, and/or urography.
- Number: treatment group: 35; control group: 35.
- Mean age of both study groups not mentioned.
- Sex, M/F: not mentioned.
- Exclusion criteria: urinary infection; anatomical alterations; multiple lithiases; urinary derivation; other factors hindering the removal of calculi.

Interventions	<p>Control group</p> <ul style="list-style-type: none"> • Standard pain medication (ibuprofen, tramadol). <p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily and same pain medication as control group. <p>Researchers emphasised that all participants should drink 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion time. • Stone expulsion rate. • Amount of analgesic consumption. • Possible complications caused by stones during the study period. • Possible side effects from medications or intolerance recorded and used for statistical analysis. • Need for hospitalisation.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Assessment of trial results was conducted at 10 days and 30 days.</p> <p>On day 30, stone expulsion was assessed by plain X-ray, ultrasonography, or urography.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "Patients were divided randomly into 2 treatment groups."</p> <p>Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.</p>
Allocation concealment (selection bias)	Unclear risk	<p>No quotes available. Insufficient information to permit judgement.</p> <p>Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quotes available. No blinding described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>
Incomplete outcome data (attrition bias)	Low risk	No quotes available.

Arrabal-Martin 2010 (Continued)

All outcomes

Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.

Selective reporting (reporting bias)

Low risk

No quotes available. Expected outcomes were reported according to objectives.

Comment: Risk of reporting bias was therefore considered to be low.

Other bias

Low risk

No quotes available. Study appears to be free of other sources of bias.

Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Autorino 2005

Methods

- Study design: single-centre RCT.
- Study duration: unclear.
- Follow-up/treatment: maximum 2-week treatment.

Participants

- Country: Italy.
- Setting: single centre.
- Patients with symptomatic ≤ 10 mm distal ureteral stones, diagnosed with NCCT.
- Number: treatment group: 50; control group: 46.
- Mean age \pm SD, years: treatment group: 46.3 ± 10.9 ; control group: 44.5 ± 11.3 .
- Sex, M/F: treatment group: 36/14; control group: 26/20.
- Exclusion criteria: UTI; severe hydronephrosis; diabetes; ulcer disease; hypotension or hypertension treated with alpha-blockers or calcium antagonists; pregnancy; multiple stones; history of spontaneous stone expulsion; ureteral stricture.

Interventions

Treatment group

- Tamsulosin 0.4 mg once daily.
- Standard therapy
 - * Diclofenac 100 mg daily.

Control group

- Standard therapy
 - * Diclofenac 100 mg daily.
- Aescin (an anti-oedema extract of the horse chestnut tree) 80 mg daily.

Outcomes

- Stone expulsion rate.
- Expulsion time.
- Need for analgesics.
- Need for hospitalisation.
- Drug side effects.

Funding sources

None stated.

Declarations of interest

None stated.

Notes

Aescin = standard therapy at this centre.

Included participants from the study by Autorino et al 2005.

Autorino 2005 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization, not blinded, was performed using a stratified permuted randomization algorithm." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants were included in the analysis; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Ayubov 2007

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: NS. • Follow-up/Treatment duration: up to 4 weeks, or until an alternative treatment was given.
Participants	<ul style="list-style-type: none"> • Country: Uzbekistan. • Setting: single centre. • Patients with distal ureteral stones. • Number: treatment group: 31; control group: 32. • Mean age \pm SD, years: NS. • Sex, M/F: NS. • Exclusion criteria: NS.
Interventions	Treatment group

Ayubov 2007 (Continued)

- Doxazosin 4 mg once daily.
- Diclofenac 75 mg on demand.

Control group

- Diclofenac 75 mg on demand.

Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Need for analgesics. • Need for hospitalisation. • Drug side effects. • Numbers and intensity of renal/ureteral colic.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Conference abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly divided into." Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Unclear risk	No quotes available. Baseline data are missing. Comment: Owing to lack of information at baseline, risk of other bias was considered to be unclear.

Bajwa 2013

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: 11 March 2011 to 11 September 2011. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Pakistan. • Setting: single centre. • Patients with lower ureteric stones. • Number: treatment group: 30; control group: 30. • Mean age \pm SD, years: overall: 33.15 ± 8.97; control group: 33.87 ± 9.61; tamsulosin group: 32.43 ± 8.33. • Sex, M/F: control group: 19/11; tamsulosin group: 18/12. • Exclusion criteria: obstruction; stone size > 1 cm; UTI.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 4 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac 50 mg on demand twice daily.
Outcomes	<ul style="list-style-type: none"> • Stone size. • Stone passage rate. • Stone expulsion time.
Funding sources	None stated.
Declarations of interest	None stated.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The patients satisfying the inclusion criteria were randomly divided in to 2 groups by random number table."</p> <p>Comment: This method of random sequence generation was considered to have low risk of bias.</p>
Allocation concealment (selection bias)	Unclear risk	<p>No quotes available. Insufficient information to permit judgement.</p> <p>Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quotes available. No blinding described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>

Bajwa 2013 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Primary outcomes were not prespecified; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Balci 2014

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: January 2010 and February 2011. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Stones in the lower one-third of the ureter. • Number: treatment group 1: 25; treatment group 2: 25; control group: 25. • Mean age \pm SD, years: 36.8 \pm 11.3 overall. • Sex, M/F: not mentioned. • Exclusion criteria: proximal or intramural part of ureteral stone; active urinary tract infection; uretero-hydronephrosis; acute renal failure; fever; multiple ureteral stones; history of surgery or endoscopic procedure of urolithiasis; chronic renal failure; diabetes mellitus; peptic ulcer; concomitant treatment with alpha-blocker and beta-blocker, calcium antagonists, or nitrates; pregnancy; lactation; patient desire for immediate stone removal.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Nifedipine 30 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac sodium 50 mg. <p>All participants were encouraged to maintain water intake of 2-2.5 L/d.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • HU of stones. • Expulsion time. • Rate of pain relief therapy. • Mean analgesic consumption. • Drug side effects.
Funding sources	None.

Balci 2014 (Continued)

Declarations of interest None.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the Power Analysis & Sample Size Software (PASS_) for Windows (NCSS Inc., Kaysville, UT). According to the software, the patients were randomly assigned to one of the following three groups." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Bayraktar 2017

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: December 2015 and May 2017. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Married male patients over the age of 18 years with opaque distal ureteral stones measuring 5–10 mm. • Number: treatment group 1: 60; sexual intercourse group 2: 66; control group: 64.

Bayraktar 2017 (Continued)

- Mean age \pm SD, years: group 1: 34.4 \pm 13.5; group 2: 38.66 \pm 14.1; group 3: 36.92 \pm 12.4.
- Sex, M/F: only male patients.
- Exclusion criteria: proximal or intermediate ureter stones (stones on the ureter-iliac artery cross); stones < 5 mm; stones \geq 10 mm; multiple ureter stones; < 18 years of age; urinary infection; fever; renal insufficiency; high creatinine level; pregnancy; severe hydronephrosis; endoscopic or open ureteral surgery history; ureteral stenosis; vesicoureteral reflux; neurogenic bladder; unmarried patients; erectile dysfunction; more than 1 sexual intercourse and masturbation statement per week for group 1 and group 3; fewer than 3 sexual intercourse statements per week for group 2.

Interventions	Treatment group 1 <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. Treatment group 2 <ul style="list-style-type: none"> • Sexual intercourse. Control group <ul style="list-style-type: none"> • As standard medical therapy, all participants were recommended daily intake of liquids to urinate at least 1.5–2 L, and 75 mg of diclofenac injected when needed for pain.
Outcomes	<ul style="list-style-type: none"> • Number of pain. • Need for pain killer injection. • Number of masturbation and sexual intercourse attempts during follow-up. • Stone expulsion rate.
Funding sources	None.
Declarations of interest	None.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "randomly divided into three groups according to the order of arrival (1:1:1 ratio)." Comment: This method of random sequence generation was considered to have high risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all tomography and direct urinary system graphy of the patients were analyzed and confirmed by a urologist blinded to the group of the patients." Comment: Risk of detection bias was considered to be low.
Incomplete outcome data (attrition bias)	Low risk	Quote: "A total of 13 patients, 6 in group 1, 4 in group 2, and 3 in group 3, were excluded from the study because they were lost in follow-up. 5 patients in

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Bayraktar 2017 (Continued)

All outcomes

group 1 and 3 patients in group 3 were also excluded from the study because they declared more than one sexual intercourse or masturbation per week."

Comment: 21/211 participants were lost to follow-up and were equally divided over the 3 groups; therefore risk of attrition bias was considered to be low.

Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives.
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Comment: Risk of reporting bias was therefore considered to be low.

Other bias	High risk	No quotes available. Only males were included in the study. Comment: Potential selection bias; therefore high risk of other bias.
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Berger 2015

Methods	<ul style="list-style-type: none"> Study design: prospective double-blind RCT. Study duration: April 2007 and February 2009. Follow-up/Treatment duration: 7 days.
Participants	<ul style="list-style-type: none"> Country: USA. Setting: single centre. All ureteral stones. Number: treatment group: 53; placebo group: 47. Mean age: treatment group: 40.62; placebo group: 44.52. Sex, M/F: treatment group: 26% male; placebo group: 30% male. Exclusion criteria: younger than 18 years; stone larger than 1 cm; infected stones; obstructing stones in solitary kidneys; currently taking Levitra, nifedipine, or steroids; requiring immediate surgical intervention; pregnant; already taking tamsulosin before enrolment.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily and standard analgesia (Vicodin and ibuprofen). <p>Placebo group</p> <ul style="list-style-type: none"> Placebo drug and standard analgesia (Vicodin and ibuprofen).
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Pain score. Drug side effects. Mean analgesic consumption.
Funding sources	None.
Declarations of interest	None.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "using a convenience sample."

Berger 2015 (Continued)

		Comment: This method of random sequence generation was considered to have high risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded, placebo-controlled." Comment: double-blind; therefore low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 127 patients enrolled during this study, 15 were lost to follow-up, and 12 received surgical intervention before the 7-day mark, leaving 100 patients for analysis." Comment: Owing to a reasonable number of participants lost to follow-up, risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Cervenakov 2002

Methods	<ul style="list-style-type: none"> • Study design: DB RCT. • Study duration: June 1999 to January 2002. • Follow-up/Treatment duration: probably 7 days.
Participants	<ul style="list-style-type: none"> • Country: Slovakia. • Setting: inpatients. • Patients, 17-76 years, with X-ray-verified lower urinary tract stones < 10 mm. • Number: treatment group: 51; control group: 53 enrolled/51 evaluated. • Age range, years: treatment group: 18-76; control group: 17-74. • Sex, M/F: treatment group: 32/19; control group: 33/18. • Exclusion criteria: pregnant women; new and decompensated diabetes mellitus; febrile state; advanced ureterohydronephroses; UTI; grave polyvalent allergies.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg. • Standard therapy. <p>Control group</p>

Cervenakov 2002 (Continued)

- Standard therapy
 - * 1 amp Tramal 50 mg – analgeticum + 1 amp diazepam 5 mg – anxiolyticum in 150 mL physiological saline infusion solution applied IV.
- These participants were also given the following per os: 3 × 2 tablets Yellon per 20 mg – antiexudativum and non-steroid antirheumatic Veral, 3 times daily per 50 mg.

All participants were made to keep a drinking regimen of at least 2.5 L of water or weak tea daily.

Outcomes	• Stone expulsion rate.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Study authors stated the study model was a double blind RCT but described no blinding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "we have applied a double blind randomized study." Comment: Randomisation was stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "As two pts. were excluded from group "A" because during treatment they developed acute obstruction pyelonephritis, both groups consisted of a rather unusual identical number of experimental and standardly treated pts. (51)." Comment: In the light of the small number of participants lost to follow-up, risk of attrition bias was stated as low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Cha 2012

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: September 2008 and June 2011. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: single centre. • One single lower ureteral stone, measuring 4-10 mm. • Number: treatment group 1: 41; treatment group 2: 30; treatment group 3: 36; control group: 34. • Mean age \pm SD, years: treatment group 1: 45.07 \pm 13.77; treatment group 2: 45.50 \pm 11.09; treatment group 3: 42.33 \pm 12.58; control group: 43.65 \pm 10.87. • Sex, M/F: treatment group 1: 31/10; treatment group 2: 20/10; treatment group 3: 25/11; control group: 18/16. • Exclusion criteria: UTI; moderate or severe hydronephrosis; hypotension; single kidney; bilateral ureteral stones; history of previous surgery on the ipsilateral ureter; currently taking an alpha-blocker, steroid, or calcium channel blocker; renal insufficiency; < 18 years of age; pregnant or lactating women.
Interventions	<p>All participants received tiroprium chloride (50 mg 3 times daily). All participants received initial treatment of 90 mg diclofenac by intramuscular injection and 5 mg cimetropium bromide by intravenous injection, with a second dose after 30 minutes or 1 hour if necessary.</p> <p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.2 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Tamsulosin 0.2 mg twice daily. <p>Treatment group 3</p> <ul style="list-style-type: none"> • Alfuzosin 10 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Solely tiroprium chloride.
Outcomes	<ul style="list-style-type: none"> • Stone size. • Stone expulsion rate. • Stone expulsion time. • Drug side effects.
Funding sources	None.
Declarations of interest	None.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was generated by using the permuted block method." Comment: This method of random sequence generation was considered to have low risk of bias.

Cha 2012 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "... was concealed from the patient-enrolling investigators (confined with a doctor assisting in the procedure but not participating in the study)." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Cho 2017

Methods	<ul style="list-style-type: none"> • Study design: double-blind placebo-controlled RCT. • Study duration: unknown. • Follow-up/Treatment duration: 90 days.
Participants	<ul style="list-style-type: none"> • Country: South Korea. • Setting: multi-centre. • Patients > 20 years of age with a single ureteral stone. The maximal diameter of the stones was 3 ± 10 mm. • Number: treatment group: 64; placebo group: 60. • Mean age ± SD, years: treatment group: 48.1 ± 14.2; placebo group: 42.33 ± 12.58. • Sex, M/F: treatment group: 49/15; placebo group: 41/19. • Exclusion criteria: presence of multiple ureter stones; renal or hepatic dysfunction; febrile urinary tract infection; breastfeeding or pregnant women; solitary kidney; hypersensitivity to naftopidil; current use of alpha-blockers, calcium channel blockers, or corticosteroid within 4 weeks; moderate to severe cardiovascular or cerebrovascular disease; significant active medical illness or genetic disorders.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Naftopidil 75 mg once daily. <p>Placebo group</p>

Cho 2017 (Continued)

- All participants received aceclofenac 100 mg or combination treatment with tramadol 37.5 mg and acetaminophen 325 mg.

Outcomes	<p>Primary outcome measures</p> <ul style="list-style-type: none"> • Stone-free rate. <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Stone-free rate at 28th day of study. • Quantity of analgesics used. • Rate of active treatment.
Funding sources	None.
Declarations of interest	None.
Notes	Participants were followed up at days 14 (visit 1), 28 (visit 2), 60 (visit 3), and 90 (visit 4) after initiation of medication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Randomization was carried out by the Medical Research Collaboration Center of Seoul National University Bundang Hospital using random permuted blocks of different sizes. The size of the next block was randomly chosen from the available block sizes."</p> <p>Comment: This method of random sequence generation was considered to have low risk of bias.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "The size of the next block was randomly chosen from the available block sizes. Randomization was stratified by each recruiting study site."</p> <p>Comment: This method of allocation concealment was considered to have low risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "One person packed the 14-day supply of tablets for each patient. All study staff at all hospitals were blinded to treatment allocation and remained blind until the end of the trial."</p> <p>Comment: double-blind; therefore low risk of bias.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>No quotes available. Figure 1 shows a detailed flow diagram of participant follow-up, including information regarding loss to follow-up, exclusion due to adverse events, or need for intervention.</p> <p>Comment: Detailed information on participant follow-up was available; risk of attrition bias was considered to be low.</p>
Selective reporting (reporting bias)	Low risk	<p>No quotes available. Expected outcomes were reported according to objectives.</p>

Cho 2017 (Continued)

Comment: Information on primary and secondary outcomes was presented in detail in the protocol at www.clinicaltrials.gov. Risk of reporting bias was therefore considered to be low.

Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.
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Doluoglu 2015

Methods	<ul style="list-style-type: none"> Study design: RCT. Study duration: September 2013 to October 2014. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Turkey. Setting: single centre. Patients with stone measuring ≤ 6 mm in the distal ureter; evaluated with KUB, US, and NCCT in selected patients. Number: treatment group: 27; control group: 30. Mean age, SD, years: treatment group: 39.3 ± 8.1; control group: 34 ± 10.4. Sex, M/F: treatment group: 27/0; control group: 30/0. Exclusion criteria: Aged < 18 years; did not have an active sexual partner; described erectile dysfunction; diabetes mellitus; a stone measuring > 6 mm; a stone located in the mid-ureter or proximal ureter (above iliac vessels); non-opaque or multiple stones; urinary tract infection; severe hydronephrosis; history of stone passage or previous endoscopic or open ureteral surgery; high serum creatinine levels; previous use of α-1-adrenergic receptor or calcium channel blockers.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> All groups received 75 mg diclofenac injections when needed. Buscopan 10 mg twice daily orally.
Outcomes	<ul style="list-style-type: none"> Stone passage rate. Time to stone passage. Number of pain episodes. Need for diclofenac injections. Number of sexual intercourse attempts.
Funding sources	None.
Declarations of interest	None.
Notes	Follow-up visits on a weekly basis with urine analysis, plain X-ray KUB, and abdominal ultrasonography.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly divided into 3 groups with the random number table envelope method."

Doluoglu 2015 (Continued)

		<p>Comment: This method of random sequence generation was considered to have low risk of bias.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "The names of the groups were written on small papers with the same size, they were folded, put in an envelope, and drawn by the patients."</p> <p>Comment: This method of allocation concealment was considered to have low risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quote available. Participants were blinded, and blinding of doctors was not described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "On follow-up, plain urinary tract x-ray images of the patients were seen and analyzed by an urologist (MFK) blinded to the group of the patients."</p> <p>Comment: Risk of detection bias was considered to be low.</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>No quote available. 13/57 participants lost to follow-up equally distributed among control and treatment groups.</p> <p>Comment: Owing to a reasonable number of participants lost to follow-up (> 20%), risk of attrition bias was considered to be high.</p>
Selective reporting (reporting bias)	High risk	<p>No quote available. No number of pain episodes described in the Results section (although this was a secondary outcome measurement). Furthermore adverse effects were predefined in Methods section and were not described in Results section.</p> <p>Comment: Owing to inconsistent reporting, risk of reporting bias was considered to be high.</p>
Other bias	Low risk	<p>No quotes available. Study appears to be free of other sources of bias.</p> <p>Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.</p>

Dong 2009

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 1 week.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: multi-centre. • Patients with ureteral stones. • Number: treatment group: 19; control group: 21. • Mean age \pm SD, years: treatment group: 54.05 \pm 12.63; control group: 45.19 \pm 12.27. • Sex, M/F: treatment group: 12/7; control group: 12/9. • Exclusion criteria: uncontrolled pain with conservative therapy; multiple stones; pregnancy; SCr \geq 2.5 mg/dL; prior ureteral surgery; urinary tract obstruction; ureteral splints.
Interventions	<p>Treatment group (group 3)</p> <ul style="list-style-type: none"> • Tamsulosin 0.2 mg.

Dong 2009 (Continued)

Control group (group 4)

- Diclofenac sodium for 1 week.

Four treatment arms, of which the first 2 underwent ESWL (groups 1 and 2); groups 3 and 4 did not want to undergo ESWL.

Outcomes	<ul style="list-style-type: none"> • Stone clearance. • Change in pain score.
Funding sources	Study was supported by research funds from Astellas Phama Korea, Inc.
Declarations of interest	None stated.
Notes	Dong Il Kang; only the abstract was written in English and therefore was interpretable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No quotes available. Comment: Participants were those who did not want to undergo ESWL; therefore risk of selection bias was considered to be high.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, risk of allocation concealment was considered to be unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

El Said 2015

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT.
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Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

El Said 2015 (Continued)

- Study duration: NS.
- Follow-up/treatment duration: 4 weeks.

Participants

- Country: Egypt.
- Setting: single centre, outpatient clinic.
- Patients with distal ureteral calculi.
- Number: treatment group: 28; control group: 26.
- Mean age \pm SD, years: treatment group: 32.8 \pm 9.5; control group: 32.1 \pm 9.2.
- Sex, M/F: treatment group: 18/10; control group: 16/10.
- Exclusion criteria: UTI; ureteral strictures; renal impairment; solitary functioning kidney; diabetes mellitus; hepatic insufficiency; severe hydronephrosis; hypotension; pregnancy; lactation; sensitivity to alpha-blockers; use of alpha-1-blockers, beta-blockers, sildenafil, ketoconazole, itraconazole, ritonavir.

Interventions

Treatment group (group 2)

- Alfuzosin 5 mg twice daily.
- Diclofenac 75 mg IM on demand.

Control group (group 1)

- Diclofenac 75 mg IM on demand.

All participants were asked to drink > 2 L of water daily and received diclofenac 75 mg IM on demand.

Outcomes

- Stone passage rate.
- Number of pain episodes.
- Pain level.
- Analgesic consumption.
- Number of hospital revisits.
- Drug adverse events.
- Complications.

Funding sources

Welcome Trust: Howard Hughes Medical Institute and others.

Declarations of interest

None.

Notes

Article 2015.

Conference abstract 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned to either the control group or the alfuzosin group based on a computer-generated random table." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.

El Said 2015 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This was a prospective, randomized, open-label, controlled study." Comment: open label trial; therefore risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "This was a prospective, randomized, open-label, controlled study." Comment: open label trial; therefore risk of detection bias was considered to be high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quote available. Comment: All participants were included in the analysis; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

El-Gamal 2012

Methods	<ul style="list-style-type: none"> • Study design: prospective DB RCT. • Study duration: October 2006 to October 2010. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Egypt. • Setting: single centre. • Patients with distal third ureteral stones. • Number: treatment group: 48; placebo group: 46. • Mean age \pm SD, years: group 1: 36.2 \pm 6; group 2: 35.3 \pm 5.7. • Sex, M/F: NS. • Exclusion criteria: UTI; ureteral strictures; renal impairment; solitary functioning kidney; pregnancy; lactation; sensitivity to alpha-blockers.
Interventions	<p>Group 1: placebo group.</p> <p>Group 2: tamsulosin group.</p> <p>Group 3: Uralyt group.</p> <p>Group 4: Uralyt and tamsulosin group.</p> <p>All participants were advised to increase fluid intake to more than 2 L per day and to receive IM injection of 75 mg of diclofenac sodium.</p>
Outcomes	<ul style="list-style-type: none"> • Mean stone size. • Analgesic needs. • Stone passage rate.
Funding sources	None stated.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

El-Gamal 2012 (Continued)

Declarations of interest	None stated.	
Notes	Non-enhanced spiral CT was done at the end of study period for all participants.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were prospectively randomized through a computer generated randomization process into four equal groups." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "The investigators and the patients were blinded to the treatment given, until the end of the study." Comment: Randomisation method was described and would not allow investigator/participant to know or influence the intervention group before eligible participant entered into the study. Therefore this method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigators and the patients were blinded to the treatment given, until the end of the study." Comment: double-blind; therefore low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "5 cases were lost to follow-up (2 in the control group and one in each of the other three groups)." Comment: Owing to the small number of participants lost to follow-up, risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Primary outcomes were not prespecified; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Erkan 2011

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: not described. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: not described. • Patients with distal third ureteral stones 4-10 mm.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Erkan 2011 (Continued)

- Number: treatment group: 37; control group: 34.
- Mean age \pm SD, years: not described.
- Sex, M/F: not described.
- Exclusion criteria: not described.

Interventions	<p>Group 1: tamsulosin group.</p> <p>Group 2: corticosteroid group.</p> <p>Group 3: tamsulosin and corticosteroid group.</p> <p>Group 4: control group.</p> <p>Data for groups 1 and 4 were used for the review.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Need for surgical intervention. • Drug adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Conference abstract.</p> <p>Follow-up on weekly basis with imaging (not discussed in detail).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "A total of 134 patients with distal ureteral stone of 4-10 mm were randomized into 4 groups."</p> <p>Comment: Randomisation stated but no information on method used was available; therefore selection bias was considered to be at unclear risk of bias.</p>
Allocation concealment (selection bias)	Unclear risk	<p>No quotes available. Insufficient information to permit judgement.</p> <p>Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quotes available. No blinding described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>No quotes available. 6 patients in control group lost to follow-up.</p> <p>Comment: losses to follow-up not balanced between treatment groups; therefore risk of attrition bias was considered to be high.</p>
Selective reporting (reporting bias)	Unclear risk	No quotes available.

Erkan 2011 (Continued)

Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.

Other bias

Unclear risk

No quotes available.

Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Erturhan 2007

Methods

- Study design: RCT.
- Study duration: December 2004 to November 2005.
- Follow-up/Treatment duration: maximum 3 weeks.

Participants

- Country: Turkey.
- Setting: single centre.
- Patients with distal ureteral stones < 10 mm.
- Number: treatment group 1: 30; treatment group 2: 30; treatment group 3: 30; control group: 30.
- Mean age (range, years): treatment group 1: 32.7 (19-41); treatment group 2: 35.8 (22-48); treatment group 3: 34.7 (24-49); control group: 31.4 (20-51).
- Sex, M/F: treatment group 1: 21/9; treatment group 2: 17/13; treatment group 3: 13/17; control group: 19/11.
- Exclusion criteria: severe hydronephrosis; a solitary kidney; an extra stone in the upper urinary system; underwent previous surgery for a urinary system stone; a non-opaque stone; diseases such as diabetes or hypertension; pregnant; renal reserve reduced by > 50%.

Interventions

Treatment group 1:

- Tamsulosin 0.4 mg daily.

Treatment group 2:

- Tamsulosin 0.4 mg daily.
- Tolterodine 2 mg, twice daily.

Treatment group 3:

- Tolterodine 2 mg, twice daily.

Control group:

- No medical treatment.

All participants were treated with prophylactic antibiotic therapy (cefuroxime axetil 250 mg (once a day)) and received 2500 mL hydration daily.

Outcomes

- Stone expulsion rate.
- Stone expulsion time.
- VAS.

Funding sources

None stated.

Declarations of interest

None stated.

Notes

Weekly checkups and follow-up with renal ultrasonography, complete urinalysis, serum urea creatinine measurements, and direct urinary system graphics.

Erturhan 2007 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After randomization to one of four groups, the patients received treatment." Comment: Owing to insufficient information, random sequence generation was considered to be at unclear risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. 5 participants were lost to follow-up; they were included in the analysis. Comment: Owing to the small number of participants lost to follow-up, risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Eryildirim 2015

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: January 2014 and January 2015. • Follow-up/Treatment duration: maximum 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Patients with ureteral stones 5-10 mm. • Number: treatment group: 60; control group: 60. • Mean age \pm SD, years: control group: 37.23 \pm 1.56; tamsulosin group: 37.07 \pm 2.26. • Sex, M/F: 84/36. • Exclusion criteria: multiple stones; previous stone-related procedures; obstruction; stent placement; congenital anomalies; active UTI; pregnancy; renal insufficiency; urgent stone removal and/or auxil-

Eryildirim 2015 (Continued)

ary procedures for intractable pain; obstruction; infection and other related complications during follow-up period.

Interventions	Control group <ul style="list-style-type: none"> Diclofenac sodium 75 mg on demand. Tamsulosin group <ul style="list-style-type: none"> Tamsulosin 0.4 mg. Diclofenac sodium 75 mg on demand.
Outcomes	<ul style="list-style-type: none"> Stone passage rate. Analgesics required. Need for stone removal procedures. Number of renal colics. Number of ED visits. HRQOL. VAS scores during pain.
Funding sources	None.
Declarations of interest	None.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization method by generating a random digit (0–60 in each group) has been used within each group." Comment: This method of random sequence generation was considered to be at low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, risk of allocation concealment was considered to be unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Losses to follow-up were not clearly described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives.

Eryildirim 2015 (Continued)

Comment: Risk of reporting bias was therefore considered to be low.

Other bias

Low risk

No quotes available. Study appears to be free of other sources of bias.

Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Ferre 2009

Methods

- Study design: RCT.
- Study duration: August 2006 to November 2007.
- Follow-up/Treatment duration: 14 days.

Participants

- Country: USA.
- Setting: ED/single centre.
- Patients > 18 years, CT-confirmed single distal ureteral stone.
- Number: treatment group: 39; control group: 41.
- Mean age \pm SD, years: treatment group: 47 \pm 14; control group: 45 \pm 12.
- Sex, M/F: treatment group: 32/6; control group: 24/15.
- Exclusion criteria: allergy or sensitivity to study drug (tamsulosin hydrochloride); sulfa/sulfonamide allergy; lithiasis of ureteral intramural tract; AKI or CKD; fever; presence of multiple ureteral stones; peptic ulcer disease; liver failure; pregnancy; breastfeeding; history of urinary surgery; history of endoscopic treatment; concomitant treatment with any of the following pharmaceuticals: -lytic drugs, calcium channel antagonists, nitrates, and vardenafil hydrochloride; inability to use study pain scale; inability to read, write, and speak English.

Interventions

Treatment group

- Tamsulosin 0.4 mg daily for 10 days.
- Standard analgesic therapy.

Control group

- Standard analgesic therapy
 - * Ibuprofen: 800 mg orally, 3 times daily.
 - * Oxycodone: 5 to 10 mg orally, every 4 to 6 hours as needed for pain.

Outcomes

- Spontaneous passage rate.
- Stone expulsion time.
- Number of episodes of colicky pain.
- Number of return visits to the ED or unscheduled primary care visits.
- Amount of opioid analgesic used.
- Number of days of missed work or inability to perform usual functions.
- Adverse events.
- Self-reported pain scores.

Funding sources

This study was funded by an academic grant from the Maine Medical Center Mentored Research Committee.

Declarations of interest

None stated.

Notes

Follow-up with all participants at 2, 5, and 14 days post discharge from the ED.

Sample size calculated.

Ferre 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was accomplished by using a table of random numbers." Comment: This method of random sequence generation was considered to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "The information on group assignment was contained in a sealed envelope within each study packet, and the envelopes were clearly labelled "do not open until informed consent is obtained." Comment: This method of allocation concealment was considered to be at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Participants lost to follow-up (4), discontinued intervention (2), excluded because the stone was located in the proximal ureter (1). Comment: Losses to follow-up were balanced across treatment groups; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Furyk 2016

Methods	<ul style="list-style-type: none"> • Study design: multi-centre, randomised DB placebo-controlled trial. • Study duration: October 2010 until March 2014. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Australia. • Setting: emergency departments. • Patients 18 years or older with symptoms suggestive of ureteric colic and a calculus demonstrated in the distal ureter on CT scan. • Number: treatment group: 202; placebo group: 201. • Median age, years (IQR): treatment group: 45.5 (35-55); placebo group: 46 (37-55). • Sex: treatment group: 78.8% men; placebo group: 84.1% men.

Furyk 2016 (Continued)

- Exclusion criteria: temperature > 38 degrees C; estimated GFR less than 60 mL/min per 1.73 m²; calculus greater than 10 mm; solitary kidney; transplanted kidney; history of ureteral stricture; known allergic reaction to study medication; current calcium channel blocker or alpha-blocker use; hypotension (systolic blood pressure < 100 mm Hg); pregnancy; planning pregnancy.

Interventions	Treatment group <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily. • Recommended regimen: indomethacin 25 to 50 mg 3 times daily orally and oxycodone 5 to 10 mg 3 times daily. Placebo group <ul style="list-style-type: none"> • Placebo drug. • Recommended regimen: indomethacin 25 to 50 mg 3 times daily orally and oxycodone 5 to 10 mg 3 times daily. Analgesia was given at the discretion of the treating physician.	
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Unplanned re-presentations to the ED or hospital admission. • Total analgesia requirements. • Pain scores measured on the verbal numerical pain scale. • Need for urological intervention. • Complications including infection, renal impairment, and days off work. • Adverse events from study drugs. 	
Funding sources	Grant from the Queensland Emergency Medicine Research Foundation.	
Declarations of interest	None stated.	
Notes	Power calculation was performed. Intention-to-treat-principle. Telephone contacts at 7, 14, 21, and 28 days with pelvic non-contrast CT at day 28.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was produced with a computer-generated program in permuted blocks of random lengths stratified by hospital and stone size." Comment: This method of random sequence generation was considered to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Once informed consent was obtained and patients were deemed appropriate for discharge, they were allocated to the next sequentially numbered study medication pack." Comment: This method of allocation concealment was considered to be at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, the treating physician, and patients were blinded to the allocation for the duration of the study and data analysis." Comment: double-blind; therefore low risk of bias.

Furyk 2016 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators, the treating physician, and patients were blinded to the allocation for the duration of the study and data analysis." Comment: Personnel responsible for outcome assessments were blinded; therefore risk of detection bias was considered to be low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Similar proportions of patients with missing and nonmissing outcome data." Comment: Missing outcome data were balanced in numbers across both groups, and reasons for missing data were similar; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Georgescu 2015

Methods	<ul style="list-style-type: none"> • Study design: randomised prospective trial. • Study duration: February 2013 and December 2013. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Romania. • Setting: single centre. • Patients 18 years or older with unilateral, non-impacted, uncomplicated ureteral stones smaller than 1 cm. • Number: treatment group 1: 50; treatment group 2: 50; control group: 50. • Mean age \pm SD, years: treatment group 1: 43.5 \pm 13.31; treatment group 2: 44.26 \pm 13.00; control group: 45.14 \pm 11.58. • Sex, M/F: treatment group 1: 27/23; treatment group 2: 31/19; control group: 26/24. • Exclusion criteria: fever; UTI; high-grade hydronephrosis; hypotension; acute or chronic renal failure; single kidney; urinary congenital anomalies; multiple or bilateral ureteral stones; history of open surgery or endoscopic procedures in the urinary tract; diabetes; peptic ulcer; concomitant treatment with alpha- or beta-blockers, calcium antagonists, steroid, nitrates; pregnant or lactating women; patients requiring immediate stone removal.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily. • Diclofenac sodium 50 mg/12 h. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Silodosin 8 mg daily. • Diclofenac sodium 50 mg/12 h. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac sodium 50 mg/12 h.

Georgescu 2015 (Continued)

Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Mean number of pain episodes. • Rates of interventions/Hospital re-admissions. • Drug adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up at 14 ± 2 days with urinalysis, KUB, and ultrasonography.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization process was achieved by means of sealed envelopes equally nominating one of the three treatment alternative." Comment: This method of random sequence generation was considered to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was performed using the SNOSE method (sequentially-numbered, opaque, sealed envelopes)." Comment: This method of allocation concealment was considered to be at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Griwan 2010

Methods	<ul style="list-style-type: none"> • Study design: randomised prospective trial. • Study duration: unknown.
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Griwan 2010 (Continued)

	<ul style="list-style-type: none"> Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: India. Setting: single centre. Patients 18 years or older with unilateral distal ureteral stones measuring 4-10 mm. Number: treatment group: 30; control group: 30. Mean age \pm SD, years: treatment group: 34.20 \pm 13.96; control group: 36.00 \pm 12.22. Sex, M/F: treatment group 2: 19/11; control group: 18/12. Exclusion criteria: all cases having active urinary tract infection; fever; acute renal failure; chronic renal failure; history of urinary surgery or endoscopic treatment; uncorrected distal obstruction; marked hydronephrosis.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg daily <p>Control group</p> <ul style="list-style-type: none"> Both groups received diclofenac 50 mg and Buscopan 10 mg orally on demand.
Outcomes	<p>Successful results were defined as complete stone passage; failure was considered if:</p> <ul style="list-style-type: none"> the participant failed to pass the stone at the end of 28 days; or uncontrolled pain and/or uroseptic fever led to hospitalisation during the study period.
Funding sources	None.
Declarations of interest	None.
Notes	Follow-up weekly with KUB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "... were divided randomly."</p> <p>Comment: Randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.</p>
Allocation concealment (selection bias)	Unclear risk	<p>No quotes available. Insufficient information to permit judgement.</p> <p>Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quotes available. No blinding described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>No quotes available.</p> <p>Comment: All participants completed the study; therefore risk of attrition bias was considered to be low.</p>

Griwan 2010 (Continued)

Selective reporting (reporting bias)	High risk	No quotes available. Comment: Outcomes were not prespecified; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Han 2006a

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: NS. • Patients with stones < 5 mm that were located in the lower ureter. • Number: treatment group: 35; control group: 32. • Mean age \pm SD, years: NS. • Sex, M/F: NS. • Exclusion criteria: UTI; hydronephrosis; pregnancy; diabetes; multiple stones; low blood pressure.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.2 mg orally once daily. <p>Control group</p> <ul style="list-style-type: none"> • Caroverine (a spasmolytic drug): 20 mg orally 3 times daily. <p>All participants were allowed 30 mg ketorolac IM injections on demand.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Use of analgesics.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Only English abstract available for judgement.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement.

Han 2006a (Continued)

		Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Losses to follow-up were not clearly described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Hermanns 2009

Methods	<ul style="list-style-type: none"> Study design: double-blind RCT. Study duration: September 2006 to September 2008. Follow-up/Treatment duration: 21 days.
Participants	<ul style="list-style-type: none"> Country: Switzerland. Setting: outpatient, single centre. Patients ≥ 18 years with single ureteral stone ≤ 7 mm below the common iliac vessels, as assessed on NCCT. Number: treatment group: 50; control group: 50. Median age, years (IQR): treatment group: 36 (30–44); control group: 41 (33–54). Sex, M/F: treatment group: 39/6; control group: 36/9. Exclusion criteria: presence of multiple ureteral stones; renal insufficiency (eGFR < 60 mL/min/1.73 m²); UTI; a solitary kidney; pregnancy; history of ureteral surgery or previous endoscopic procedures; hypersensitivity to tamsulosin or current alpha-blocker, calcium antagonist, or corticosteroid medication.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> Placebo.
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Time to stone passage. Required total amount of analgesic.

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Hermanns 2009 (Continued)

- Reported maximum daily pain score until stone expulsion.
- Intervention rate.
- Safety of therapy.

Funding sources	None.
Declarations of interest	None.
Notes	Sample size calculated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Enrolled patients underwent randomisation in a 1:1 fashion in blocks of 10 to receive either a daily single dose of tamsulosin (0.4 mg) or placebo. The sequence of randomisation was computer generated and was performed by the university hospital pharmacy using DatInF Randlist software v.1.0 (DatInF GmbH, Tübingen, Germany)." Comment: This method of random sequence generation was considered to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation data were kept strictly confidential in sealed envelopes, accessible only to the primary and senior investigator." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patient, the attending urologist were not aware of study arm assignments until the final assessment of outcome." Comment: double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Personnel responsible for outcome assessments were blinded." Comment: double-blind; therefore low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patients were included in the final analysis on an intention-to-treat basis. Patients who experienced stone expulsion before first medication, who withdrew their consent, or who were lost to follow-up were excluded from the analysis." Comment: missing outcome data and losses to follow-up balanced in numbers across both groups; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Hong 2008

Methods	<ul style="list-style-type: none"> • Study design: clinical trial (unknown type). • Study duration: January 2004 and September 2007. • Follow-up/Treatment duration: 2 weeks.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: NS. • Patients with symptomatic distal ureteral stones. • Number: treatment group 1: 42; treatment group 2: 66; treatment group 3: 72. • Mean age \pm SD, years: NS. • Sex, M/F: NS. • Exclusion criteria: NS.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Furosemide 40 mg daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Furosemide 40 mg daily. • Tamsulosin 0.4 mg daily. <p>Treatment group 3</p> <ul style="list-style-type: none"> • Furosemide 40 mg daily. • Tamsulosin 0.4 mg daily. • Deflazacort 24 mg daily.
Outcomes	<ul style="list-style-type: none"> • Stone passage rate. • Time spent for stone-expulsion. • Adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Conference abstract.</p> <p>Follow-up time: 2 weeks, visits at 1st and 2nd weeks after medication.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.

Hong 2008 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	No quotes available. 61 patients excluded from the study; no details available. Comment: large number of patients excluded from the study without clarification. Therefore, risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Unclear risk	No quotes available. No information on baseline data. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Ibrahim 2013

Methods	<ul style="list-style-type: none"> Study design: prospective RCT. Study duration: July 2012 and December 2012. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Iraq. Setting: single centre. Symptomatic ureteric stone < 10 mm in diameter. Number: treatment group 1/study group II: 40; treatment group 2/study group III: 40; control group/study group I: 32. Mean age \pm SD, years: study group I: 36.71 \pm 11.64; study group II: 38.17 \pm 14.54; study group III: 36.5 \pm 11.54. Sex, M/F: study group I: 25/7; study group II: 32/8; study group III: 34/6. Exclusion criteria: acute infection; a solitary kidney; elevated levels in renal functional tests at presentation; severe hydronephrosis; bilateral ureteric stones; pregnancy or lactation; current use of alpha-blockers, calcium channel blockers, or steroids; age < 18 years; any allergic reaction to study medication.
Interventions	<p>Control group/Study group I</p> <ul style="list-style-type: none"> Diclofenac potassium orally 50 mg and/or diclofenac sodium as an IM injection of 75 mg on demand. <p>Treatment group 1/Study group II</p> <ul style="list-style-type: none"> Tamsulosin: 0.4 mg daily. Diclofenac potassium orally 50 mg and/or diclofenac sodium as an IM injection of 75 mg on demand. <p>Treatment group 2/Study group III</p> <ul style="list-style-type: none"> Alfuzosin 10 mg daily. Diclofenac potassium orally 50 mg and/or diclofenac sodium as an IM injection of 75 mg on demand.
Outcomes	<ul style="list-style-type: none"> Stone passage rate. Stone expulsion time. Drug adverse events.

Ibrahim 2013 (Continued)

Funding sources	None.
Declarations of interest	None.
Notes	Follow-up weekly for 4 weeks; every visit focussed history, physical examination, and urinary US.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised systematically at a ratio of 1:1." Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	No quotes available. Comment: Numbers of participants lost to follow-up in the different study groups were not equally distributed; therefore risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Islam 2010

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: July 2007 to December 2008. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Bangladesh. • Setting: NS. • Distal ureteral stones (juxtavesical tract and ureterovesical junction), 1 cm or smaller. • Number: treatment group 1: 33; treatment group 2: 33; control group: 32.

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Islam 2010 (Continued)

- Mean age, years: treatment group 1: 46.6; treatment group 2: 47.4; control group: 42.8.
- Sex, M/F: treatment group 1: 20/12; treatment group 2: 21/10; control group: 17/11.
- Exclusion criteria: UTI; severe hydronephrosis; a solitary kidney; extra stone in the upper urinary system; underwent previous surgery for a urinary system stone; a non-opaque stone; diseases such as diabetes or hypertension; pregnant women; those whose renal reserve was reduced by more than 50%.

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily. • Ciprofloxacin 500 mg, twice a day. • Diclofenac sodium for routine use during pain episodes. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Nifedipine 20 mg daily (slow-release preparation). • Ciprofloxacin 500 mg, twice a day. • Diclofenac sodium for routine use during pain episodes. <p>Control group</p> <ul style="list-style-type: none"> • Ciprofloxacin 500 mg, twice a day. • Diclofenac sodium for routine use during pain episodes. <p>All participants received 2500 mL hydration daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone passage rate. • Stone expulsion time. • Stone size. • Mean diclofenac sodium dosage. • Drug adverse events. • Hospitalisation.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up weekly with renal ultrasonography, X-ray KUB, urinalysis, and serum creatinine measurements.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.

Islam 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: Low percentage of loss to follow-up in each group (< 5%); therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Mean diclofenac sodium dosage and drug adverse events were not described as outcome parameters in the Methods section; therefore risk of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Itoh 2011

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: NS. • Follow-up/Treatment duration: 8 weeks.
Participants	<ul style="list-style-type: none"> • Country: Japan. • Setting: single centre. • Symptomatic unilateral ureteral calculi smaller than 10 mm. • Number: control group: 92; treatment group: 89. • Mean age, years: NS. • Sex, M/F: NS. • Exclusion criteria: NS.
Interventions	<p>Control group</p> <ul style="list-style-type: none"> • Pain medication (drug type and dosage not described). <p>Treatment group</p> <ul style="list-style-type: none"> • Silodosin 8 mg daily. <p>All participants were instructed to drink 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Need for analgesics (not described in Results section). • Drug adverse events (not described in Materials and Methods section).
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Conference abstract.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Itoh 2011 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to be at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Loss to follow-up was not described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	High risk	No quotes available. Need for analgesics was one of the outcome parameters but was not described in Results section. Adverse events were described in Results section but were not stated as one of the outcome parameters. Comment: Owing to inconsistency in describing outcome parameters, risk of reporting bias was considered to be high.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Itoh 2013

Methods	<ul style="list-style-type: none"> Study design: prospective RCT. Study duration: March 2010 to August 2010. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Japan. Setting: single centre. Symptomatic men with unilateral distal ureteral calculi smaller than 10 mm. Number: control group: 56; treatment group: 56. Mean age \pm SD, years: control group: 55.8 \pm 10.4; treatment group: 56.3 \pm 11.7. Sex, M/F: only male patients. Exclusion criteria: UTI; severe hydronephrosis; diabetes; ulcers; hypotension; renal dysfunction; multiple stones or ureteral stricture.

Itoh 2013 (Continued)

Interventions	Study group A/Control group <ul style="list-style-type: none"> Diclofenac sodium suppository 50 mg. Study group B/Treatment group <ul style="list-style-type: none"> Silodosin 8 mg daily. Diclofenac sodium suppository 50 mg. All participants were instructed to drink 2 L of water daily.
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Stone size. Need for analgesics. Drug adverse events.
Funding sources	None stated.
Declarations of interest	None.
Notes	Diagnostics for follow-up were not described. Conference abstract in 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly divided into two groups by using a random number table envelope method." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: 1 participant lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.

Itoh 2013 (Continued)

Other bias	High risk	<p>No quotes available. Stone size was significantly different between the 2 study groups. Furthermore, only men were included in the study.</p> <p>Comment: Owing to potential selection bias, we considered judgement as having high risk of bias.</p>
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Kaneko 2010

Methods	<ul style="list-style-type: none"> • Study design: prospective randomised study. • Study duration: November 2005 to August 2006. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Japan. • Setting: single centre. • Males with symptomatic ureteral stones, 10 mm or smaller, diagnosed with X-ray, US, and NCCT, when necessary. • Number: treatment group: 31; control group: 34. • Mean age \pm SD, years: treatment group: 50 \pm 8.8; control group: 45 \pm 8.7. • Sex, M/F: all male. • Exclusion criteria: UTI; severe hydronephrosis; multiple stones; hypotension; ureteral stricture; current use of calcium antagonist or alpha-adrenergic blockers.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.2 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Watchful waiting. <p>50 mg diclofenac suppository on demand for all participants.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Total diclofenac dosage.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Follow-up: maximum of 4 weeks, weekly or biweekly X-ray and US.</p> <p>Sample size was arbitrarily determined and was not based on statistical calculation.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "patients were randomly allocated into two treatment groups by using a random number table."</p> <p>Comment: This method of random sequence generation was considered to have low risk of bias.</p>
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement.

Kaneko 2010 (Continued)

		Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: 6 participants were excluded from the study and were balanced between intervention groups; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Kim 2007b

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: single centre. • Patients who were diagnosed with ureteral stones < 10 mm. • Number: treatment group: 34; control group: 42. • Mean age ± SD, years: treatment group: 40.7 ± 11.1; control group: 45.7 ± 13.8. • Sex, M/F: treatment group: 24/10; control group: 24/18. • Exclusion criteria: NS.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin: 0.2 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • NSAID for pain. <p>All participants were instructed to ingest at least 2 L of fluids daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone clearance. • Expulsion time. • ED visit for pain control.

Kim 2007b (Continued)

Funding sources	None stated.	
Declarations of interest	None stated.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Loss to follow-up was not described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Kupeli 2004

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: February 2003 and March 2004. • Follow-up/Treatment duration: 15 days.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Patients who had lower ureteral stones within the distal 5 cm of the ureter, assessed by KUB, intravenous pyelography, CT, and US when necessary. • Number: treatment group: 15; control group: 15.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Kupeli 2004 (Continued)

- Mean age, years (range): treatment group: 41.9 (23–63); control group: 43.74 (21–65).
- Sex, M/F: 56/22 (total study).
- Exclusion criteria: signs and symptoms of UTI; pregnancy; severely impacted stones; multiple stones; non-opaque stones; severe hydronephrosis; hepatic dysfunction; non-functioning kidney; treatment with calcium antagonists; morbid obesity.

Interventions	Treatment group (group 2) <ul style="list-style-type: none"> • Conventional treatment. • Tamsulosin 0.4 mg daily orally for 15 days. Control group (group 1) <ul style="list-style-type: none"> • Conventional treatment <ul style="list-style-type: none"> * Oral hydration. * Diclofenac sodium 100 mg daily orally for 15 days. Four-arm study, of which groups 3 and 4 underwent SWL.
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Side effects.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up only at the 15th day (last day of study) with plain abdominal X-ray and helical CT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the coin method." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patient follow-up examinations were performed by two of us who were unaware of the treatment received." Comment: Investigators evaluating follow-up examinations were blinded; therefore risk of detection bias was considered to be low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants were lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Kupeli 2004 (Continued)

Comment: Risk of reporting bias was therefore considered to be low.

Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.
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Lee 2014

Methods	<ul style="list-style-type: none"> Study design: prospective open-label RCT. Study duration: July 2010 to August 2012. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Korea. Setting: 2 university hospitals. Patients 18 years or older with renal colic and a single, unilateral, radiopaque, proximal ureteral calculus smaller than 7 mm. Number: treatment group: 54; control group: 54. Mean age \pm SD, years: treatment group: 43.6 \pm 12.4; control group: 47.9 \pm 11.4. Sex, M/F: treatment group: 33/54; control group: 35/54. Exclusion criteria: ureteral calculi > 6 mm; multiple ureteral calculi; febrile urinary tract infection; single kidney; non-functioning kidney; pregnancy; azotaemia; ureteral stricture; severe hydronephrosis; current treatment with medications that could affect stone passage, such as alpha-blockers, calcium channel blockers, steroids, or nitrates; desire for immediate stone removal because of colic.
Interventions	<p>Study group A/Control group</p> <ul style="list-style-type: none"> Ultracet ER (pain medication). <p>Study group B/Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.2 mg once daily. Ultracet ER (pain medication). <p>All participants were asked to drink 2 L water daily.</p>
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Time to stone passage. Post-trial EuroQOL score. Oral analgesic requirements. Drug adverse events.
Funding sources	None.
Declarations of interest	None.
Notes	Sample size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A predefined randomization sequence was created by a computer random number generator using a block size of 4."

Lee 2014 (Continued)

		Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This prospective, randomized, open-label, multicenter trial." Comment: Open-label trial is considered to have high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	No quotes available. Comment: significant number of participants lost to follow-up. Loss to follow-up was not balanced between intervention groups; therefore risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Liatsikos 2007

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: 1 January to 30 April 2005. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Greece. • Setting: single centre. • Patients with distal ureteral stone < 10 mm, assessed with KUB and US. • Number: <ul style="list-style-type: none"> * Stones < 5 mm: treatment group 1: 20; control group 1: 15. * Stones 5-10 mm: treatment group 2: 22; control group 2: 16. • Mean age \pm SD, years: <ul style="list-style-type: none"> * Stones < 5 mm: treatment group 1: 47.50 \pm 10.33; control group 1: 46.33 \pm 10.74. * Stones 5-10 mm: treatment group 2: 47.32 \pm 9.20; control group 2: 43.75 \pm 11.16. • Sex, M/F: <ul style="list-style-type: none"> * Stones < 5 mm: treatment group 1: 11/9; control group 1: 6/9. * Stones 5-10 mm: treatment group 2: 12/10; control group 2: 7/9. • Exclusion criteria: UTI; severe hydronephrosis; radiolucent stones; previous ureteral surgery; diabetes; peptic ulcer; pregnancy; hypotension; calcium antagonist; history of spontaneous stone expulsion; pyeloureteral colic for more than a day; already received treatment for ureteral colic.

Liatsikos 2007 (Continued)

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Doxazosin 4 mg daily for 4 weeks. <p>Control group 1</p> <ul style="list-style-type: none"> • No treatment. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Doxazosin 4 mg daily for 4 weeks. <p>Control group 2</p> <ul style="list-style-type: none"> • No treatment. <p>All participants were advised to consume at least 2 L of water daily and were allowed to use symptomatic therapy of 75 mg of diclofenac on demand.</p>
Outcomes	<ul style="list-style-type: none"> • Stone passage. • Number of pain episodes. • Total diclofenac dosage (not mentioned in Results section). • Time to spontaneous passage of stone. • Blood pressure. • Side effects.
Funding sources	None stated.
Declarations of interest	None stated.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	<p>Quote: "The type of therapy (doxazosin or not) was determined according to the day the patient presented to the hospital, with every patient who presented on odd-numbered days being assigned to take doxazosin."</p> <p>Comment: This method of random sequence generation was considered to have high risk of bias.</p>
Allocation concealment (selection bias)	High risk	<p>No quotes available. Open random allocation schedule.</p> <p>Comment: This method of allocation concealment was considered to have high risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "unblinded."</p> <p>Comment: no blinding; therefore risk of performance bias was considered to be high.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>No quotes available. No blinding of outcome assessments described.</p> <p>Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.</p>
Incomplete outcome data (attrition bias)	Low risk	No quotes available.

Liatsikos 2007 (Continued)

All outcomes

Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.

Selective reporting (reporting bias)

High risk

No quotes available.

Comment: Although mentioned as outcome measurement in the Methods section, total dosage of diclofenac use was not described in the Results section; therefore risk of reporting bias was considered to be high.

Other bias

Low risk

No quotes available. Study appears to be free of other sources of bias.

Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Lojanapiwat 2008

Methods

- Study design: RCT.
- Study duration: 10 January to 9 July 2006.
- Follow-up/Treatment duration: 28 days.

Participants

- Country: Thailand.
- Setting: multi-centre.
- Patients with distal ureteral stone 4-10 mm, measured by KUB.
- Number: treatment group 1: 25; treatment group 2: 25; control group: 25.
- Mean age \pm SD, years: treatment group 1: 48.00 \pm 15.74; treatment group 2: 46.71 \pm 12.20; control group: 46.52 \pm 13.63.
- Sex, M/F: treatment group 1: 15/10; treatment group 2: 20/5; control group: 20/5.
- Exclusion criteria: UTI; severe hydronephrosis; history of ureteric surgery.

Interventions

Treatment group 1

- Tamsulosin 0.2 mg once daily for a maximum of 28 days.
- Standard therapy.

Treatment group 2

- Tamsulosin 0.4 mg once daily for a maximum of 28 days.
- Standard therapy.

Control group

- Standard therapy
 - * Diclofenac 50 mg twice daily for 10 days.

If participants developed renal colic during treatment, they were given an IM injection of 75 mg diclofenac in the emergency department.

Outcomes

- Stone expulsion rate.
- Stone expulsion time.
- Number of diclofenac injections.
- Side effects.

Funding sources

Astellas Pharma (Thailand).

Declarations of interest

None.

Alpha-blockers as medical expulsive therapy for ureteral stones (Review)

Lojanapiwat 2008 (Continued)

Notes Sample size calculated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomized in three groups by the assistant nurse." Comment: This method of random sequence generation was considered to have unclear risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No quote available. Comment: no blinding; therefore risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Lojanapiwat 2012

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Thailand. • Setting: single centre. • Patients with single radio-opaque proximal ureteral stone 4-10 mm. • Number: control group: 21; treatment group: 21. • Mean age \pm SD, years: NS. • Sex, M/F: NS. • Exclusion criteria: NS.
Interventions	Control group/Study group I

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Lojanapiwat 2012 (Continued)

- Oral sodium diclofenac 50 mg twice a day for 10 days.
- Diclofenac 75 mg IM on demand.

Tamsulosin group/Study group 2

- Tamsulosin 0.4 mg once daily for a maximum of 28 days.
- Oral sodium diclofenac 50 mg twice a day for 10 days.
- Diclofenac 75 mg IM on demand.

Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone relocation rate. • Colic episode. • Additional treatment.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Conference abstract.</p> <p>Data on stone clearance and stone relocation rate at 4 weeks were not described separately.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Loss to follow-up was not described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Unclear risk	No quotes available.

Lojanapiwat 2012 (Continued)

Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Maitra 2012

Methods	<ul style="list-style-type: none"> Study design: prospective placebo-controlled RCT. Study duration: January 2006 to December 2010. Follow-up/Treatment duration: 6 weeks.
Participants	<ul style="list-style-type: none"> Country: India. Setting: single centre. Adults aged 18 or older, stones smaller than 10 mm located in the distal ureter (in an area extending from the lower border of the S-1 joint to the ureterovesicular junction). Number: treatment group 1/tamsulosin group: 50; treatment group 2/tamsulosin and nifedipine group: 50; placebo group: 50. Mean age \pm SD, years: treatment group 1: 32.7, no SD; treatment group 2: 36.4, no SD; placebo group: 39.2, no SD. Sex, M/F: treatment group 1: 39/11; treatment group 2: 40/10; placebo group: 37/13. Exclusion criteria: desire to treat colic; gross back pressure changes; recurrent urinary tract infection; ischaemic heart disease; history of previous surgery in the distal ureter; acute renal failure.
Interventions	<p>Treatment group 1/tamsulosin group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg daily. <p>Treatment group 2/tamsulosin + nifedipine group</p> <ul style="list-style-type: none"> Nifedipine 5 mg twice daily. Tamsulosin 0.4 mg daily. <p>Placebo group</p> <ul style="list-style-type: none"> Diclofenac and Buscopan - not described in detail.
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Time to stone passage. Number of colic episodes. Need for analgesics and anti-spasmodic treatment.
Funding sources	None stated.
Declarations of interest	None.
Notes	Follow-up weekly with KUB and US.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement.

Maitra 2012 (Continued)

		Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Occurrence of adverse effects was not predefined as outcome measurement. Time to stone expulsion was not measured with SDs. Number of colic episodes was not specified. Analgesic use was not described in detail (no SDs given). Comment: inconsistency in describing outcome measurements; therefore risk of bias was considered to be high.
Other bias	High risk	No quotes available. Comment: questionable whether this study was placebo-controlled based on information provided in the Methods section; therefore risk of other sources of bias was considered to be unclear.

Meltzer 2017

Methods	<ul style="list-style-type: none"> • Study design: double-blind multi-centre placebo-controlled RCT. • Study duration: 2013-2016. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: USA. • Setting: multi-centre, GWU Hospital, Hospital at University of Pennsylvania/Thomas Jefferson University Hospital, University of Pittsburgh Medical Center, University of Alabama at Birmingham Medical Center (2015). • Inclusion criteria: age \geq 18 years, symptoms consistent with renal colic, evidence of ureterolithiasis on CT at time of ED presentation, largest stone dimension $<$ 9 mm, no prior GU surgery, not admitted to hospital/no urinary tract infection, telephone access for follow-up contact. • Number: treatment group 1/tamsulosin group: 267; placebo group: 245. • Mean age \pm SD, years: treatment group 1: 41.8 ± 13.6; placebo group: 39.3 ± 12.9. • Sex, M/F: treatment group 1: 197/70; placebo group: 176/69. • Exclusion criteria: patient desiring or requiring immediate surgical intervention and thus not a candidate for outpatient kidney stone management; current urinary tract infection based on urine dipstick as admission and urgent procedural management are likely indicated; known anatomical genitourinary abnormalities or prior GU surgeries; positive pregnancy test making proper radiological imaging contraindicated; breastfeeding mothers; history of hypersensitivity to tamsulosin; current use of alpha-blockers or calcium channel blockers; current use of steroids, which may have an independent effect on stone expulsion; spontaneous stone expulsion before enrolment; largest stone dimension \geq 9 mm assessed by radiological imaging; very unlikely to pass spontaneously; presence of stone in the bladder; current use of vardenafil, which is tamsulosin contraindicated; ipsilateral, transplanted,

Meltzer 2017 (Continued)

or solitary kidney as hospitalisation may be necessary; known renal insufficiency; fever defined as > 101.5°F, which may indicate infection; floppy iris syndrome, which is tamsulosin contraindicated; planned cataract surgery in the next 60 days, which is tamsulosin contraindicated; prisoners/wards of state; prior enrolment in STONE (candidates who are screened and found ineligible may be rescreened at a later date).

Interventions	Treatment group 1/tamsulosin group <ul style="list-style-type: none"> Tamsulosin 0.4 mg daily. Placebo group.
Outcomes	<ul style="list-style-type: none"> Primary outcome: stone expulsion by 28 days as reported by patient. Secondary outcomes: ED visits or other hospitalisations, surgical interventions or lithotripsy, stone passage confirmation on CT scan, cross-over to open-label tamsulosin, length of time in pain, cost savings, time until stone expulsion, total amounts of analgesia taken, days of work lost.
Funding sources	Research reported in this abstract was supported by National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number 3 U01 DK 096037. Content is solely the responsibility of the trial authors and does not necessarily represent the official views of the National Institutes of Health.
Declarations of interest	None.
Notes	5 telephone calls during trial period (day 2, day 7, day 15, day 20, day 29). Follow-up CT in a certain group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No quotes available. Blinding of both participants and personnel. Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: Only a small number of participants were lost to follow-up with clear description; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Unclear risk	No quotes available.

Meltzer 2017 (Continued)

Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.

Other bias

Unclear risk

No quotes available.

Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Mshemish 2012

Methods

- Study design: prospective single-blind RCT.
- Study duration: January to May 2011.
- Follow-up/Treatment duration: 45 days.

Participants

- Country: Iraq.
- Setting: single centre.
- All male and female patients ≥ 18 years presenting with acute renal colic were evaluated for study participation. Patients with a single ureteral stone ≤ 10 mm below the common iliac vessels were eligible for inclusion in the study.
- Number: treatment group 1/tamsulosin group: 33; treatment group 2/doxazosin group: 33; control group: 34.
- Mean age \pm SD, years: treatment group 1: 44.3 ± 12.5 ; treatment group 2: 45.1 ± 11.6 ; control group: 43.8 ± 13.2 .
- Sex, M/F: treatment group 1: 23/10; treatment group 2: 21/12; control group: 24/10.
- Exclusion criteria: presence of multiple ureteral stones; hydronephrosis; renal dysfunction; urinary tract infection; a solitary kidney; pregnancy; history of ureteral surgery or previous endoscopic procedures; hypersensitivity to α -blocker; current α -blocker, calcium antagonist, or corticosteroid.

Interventions

Treatment group 1/tamsulosin group

- Tamsulosin 0.4 mg daily.

Treatment group 2/doxazosin group

- Doxazosin 4 mg daily.

Control group

- First treatment with meloxicam (15 mg) by IM injection, with a second dose after 30 minutes if necessary.

Outcomes

- Stone expulsion rate.
- Stone expulsion time.
- Frequency of pain attacks.
- Complications of medication.

Funding sources

None stated.

Declarations of interest

None stated.

Notes

Follow-up weekly with urine analysis, serum creatinine measurement, KUB, and US NCCT at the end of the study.

Risk of bias
Bias
Authors' judgement
Support for judgement

Mshemish 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. Blinding was not described in detail. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	No quotes available. Comment: no intention-to-treat analysis used and 5 participants lost to follow-up; therefore risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	High risk	No quotes available. Comment: Owing to incorrect data for stone clearance stratified for stone size, information is not interpretable and risk of other sources of bias was considered to be high.

Mukhtarov 2007

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Uzbekistan. • Setting: single centre. • Patients with distal ureteral stones. • Number: <ul style="list-style-type: none"> * Stones < 6 mm: treatment group 1: 27; control group 1: 25. * Stones ≥ 6 mm: treatment group 2: 24; control group 2: 21. • Mean age ± SD, years: NS. • Sex, M/F: 61/36. • Exclusion criteria: NS.
Interventions	Treatment group 1 <ul style="list-style-type: none"> • Doxazosin 4 mg daily. • Standard regimen.

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Mukhtarov 2007 (Continued)

Control group 1

- Standard regimen
 - * Oral hydration and diclofenac sodium on demand.

Treatment group 2

- SWL.
- Doxazosin 4 mg daily.
- Standard regimen.

Control group 2

- SWL.
- Standard regimen.

Outcomes	<ul style="list-style-type: none"> • Stone-free rate. • Stone expulsion time. • Pain scores. • Mean diclofenac consumption in mg.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Conference abstract.</p> <p>Maximum follow-up in group 1: 28 days.</p> <p>Weekly re-evaluation with X-ray and US.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants lost to follow-up; therefore risk of attrition bias was considered to be low.

Mukhtarov 2007 (Continued)

Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered to be unclear.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Ochoa-Gomez 2011

Methods	<ul style="list-style-type: none"> Study design: double-blind RCT. Study duration: June 2006 to December 2007. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: Mexico. Setting: single centre, ED. Patients older than 18 years with distal reno-ureteral stones between 5 and 10 mm. Number: treatment group/study group A: 32; placebo group/study group B: 33. Mean age \pm SD, years: treatment group: 38.5 \pm 11.3; placebo group: 38.2 \pm 12.4. Sex, M/F: treatment group: 15/17; placebo group: 21/12. Exclusion criteria: hydronephrosis; acute or chronic renal insufficiency; multiple ureteral lithiasis; history of surgery or endourological procedures; large and impacted ureteral calculi; pregnancy; lactation; distal ureteral lithiasis in a single kidney; taking alpha- or beta-blockers; nitrates of calcium antagonists; patients who worked as airline pilots.
Interventions	<p>Study group A/Treatment group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg daily. Standard regimen (not described). <p>Study group B/placebo group</p> <ul style="list-style-type: none"> Placebo drug. Standard regimen (not described). <p>All participants were instructed to drink at least 2 L of water per day and to carry out normal activities.</p>
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Stone size. Drug adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up every 14 days with plain abdominal film and abdominal ultrasonogram.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Ochoa-Gomez 2011 (Continued)

Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No quotes available. Blinding of both participants and personnel. Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. No imaging at the end of follow-up was done to evaluate stone clearance. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Park 2012

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Korea. • Setting: NS. • Patients with a single proximal ureteral calculus smaller than 7 mm. • Number: study group A/control group: 30; study group B/treatment group: 30. • Mean age \pm SD, years: NS. • Sex, M/F: NS. • Exclusion criteria: NS.
Interventions	<p>Study group A/control group</p> <ul style="list-style-type: none"> • Oral hydration > 2 L/d. <p>Study group B/treatment group</p> <ul style="list-style-type: none"> • Oral hydration > 2 L/d.

Park 2012 (Continued)

	<ul style="list-style-type: none"> Tamsulosin 0.2 mg/d.
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Patient QOL. Stone size.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up weekly with KUB or CT. Primary endpoint was cumulative stone passage rate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Not all participants received CT scan at the end of the trial period. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	No quotes available. Comment: a significant number of participants lost to follow-up (20%-30%); therefore risk of attrition bias was considered to be high.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Pedro 2008

Methods	<ul style="list-style-type: none"> Study design: RCT. Study duration: January 2005 to June 2007.
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Pedro 2008 (Continued)

	<ul style="list-style-type: none"> Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: USA. Setting: single centre. Patients from the ED with renal colic secondary to a distal ureteral stone. Number: treatment group: 34; control group: 35. Mean age \pm SD, years: treatment group: 36.69 \pm 13.06; control group: 42.03 \pm 12.85. Sex, M/F: treatment group: 28/6; control group: 27/8. Exclusion criteria: stones > 8 mm on stone protocol CT; renal insufficiency (SCr > 1.8 mg/dL); a solitary kidney and UTI; concomitant use of alpha-blocker; pregnancy; history of ureteral stricture; allergic reaction to study medication.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Alfuzosin: 1 pill daily after breakfast until the stone was passed; dose not stated. <p>Control group</p> <ul style="list-style-type: none"> Placebo: 1 pill daily after breakfast until the stone was passed.
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Use of analgesics. Pain scores. Side effects.
Funding sources	Sanofi-Aventis Pharmaceuticals.
Declarations of interest	None stated.
Notes	Sample size calculated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... using a random number assignment. A computerized random number generator was used." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	No quotes available. Comment: Allocation was concealed; therefore the allocation method was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators were blinded to the randomization scheme and patients and investigators were blinded to medication until termination of the study." Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.

Pedro 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. 7 patients excluded: stone passage before first dose in 4 and withdrawal of consent in 3. Comment: small number of participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Pickard 2015

Methods	<ul style="list-style-type: none"> Study design: DB RCT. Study duration: 11 January 2011 and 20 December 2013. Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> Country: UK. Setting: multi-centre. Adults aged 18-65 years with 1 stone measuring 10 mm or less (at largest dimension) in ureter identified on CT KUB. Number: treatment group 1/tamsulosin group: 378; treatment group 2/nifedipine group: 379; placebo group: 379. Mean age \pm SD, years: treatment group 1: 43.1 \pm 11.5; treatment group 2: 42.3 \pm 11.0; placebo group: 42.8 \pm 12.3. Sex, M/F: treatment group: 315/68; treatment group 2: 317/66; placebo group: 299/85. Exclusion criteria: known or suspected pregnancy (confirmed by a pregnancy test); women who were breastfeeding; asymptomatic incidentally found ureteric stone; stone not previously confirmed by CT KUB; stone with any single dimension > 10 mm; kidney stone without the presence of ureteric stone; multiple (i.e. \geq 2) stones within ureter; bilateral ureteric stones; stone in a ureter draining a solitary kidney (anatomically or functionally); abnormal renal tract anatomy; presence of urinary sepsis; chronic kidney disease stage 4 or 5; currently taking an alpha-blocker; currently taking a calcium channel blocker; currently taking PDE5 inhibitors; contraindication or allergy to tamsulosin or nifedipine; inability to understand or complete trial documentation.
Interventions	<p>Treatment group 1/tamsulosin group</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg daily until the stone was passed, need for intervention was agreed, or 4 weeks had passed since randomisation. <p>Treatment group 2/nifedipine group</p> <ul style="list-style-type: none"> Nifedipine 30 mg daily until the stone was passed, need for intervention was agreed, or 4 weeks had passed since randomisation. <p>Control group</p> <ul style="list-style-type: none"> Placebo: 1 pill daily until the stone was passed, need for intervention was agreed, or 4 weeks had passed since randomisation. <p>Standard pain medication - not described in detail.</p>

Pickard 2015 (Continued)

Outcomes	Primary outcome measurements <ul style="list-style-type: none"> Stone expulsion rate. Reduction in incremental cost per QALY gained at 12 weeks. Secondary outcome measurements <ul style="list-style-type: none"> Pain scores. Time to stone passage. Participant-reported discontinuation of trial medications. NHS primary and secondary care use and costs up to 3 months.
Funding sources	UK National Institute for Health Research Health Technology Assessment Programme.
Declarations of interest	Trial author JN is a member of the HTA commissioning board and the NIHR HTA and Efficacy and Mechanism Evaluation editorial board. All other trial authors declare no competing interests.
Notes	Sample size calculation. Follow-up at 4 and 12 weeks with questionnaires, case report forms during clinical visits, or telephone contact.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... by a remote randomisation system." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "... supplied by an independent Source." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, clinicians, and trial personnel remained unaware of the allocated group." Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No quotes available. Comment: Personnel responsible for outcome assessments were blinded; therefore risk of detection bias was considered to be low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: Small number of participants lost to follow-up equally balanced between treatment groups; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Unclear risk	No quotes available.

Pickard 2015 (Continued)

Comment: Time to stone passage was evaluated in only a small portion of the study group (potential selection bias); therefore risk of other bias was considered to be unclear.

Porpiglia 2006

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: January 2004 to September 2005. • Follow-up/Treatment duration: 10 days.
Participants	<ul style="list-style-type: none"> • Country: Italy. • Setting: single centre. • Patients with symptomatic distal ureteral stones > 4 mm, recruited from ED, diagnosed with KUB/US or CT if necessary. • Number: treatment group 1: 33; treatment group 2: 24; treatment group 3: 33; control group: 24. • Mean age \pm SD, years: treatment group 1: 47.8 \pm 1.3; treatment group 2: 45.3 \pm 2.2; treatment group 3: 48.2 \pm 0.6; control group: 45.2 \pm 0.88. • Sex, M/F: treatment group 1: 17/16; treatment group 2: 20/4; treatment group 3: 23/10; control group: 12/12. • Exclusion criteria: fever; high-grade hydronephrosis; diabetes; gastric ulcer; pregnancy; hypotension; history of spontaneous stone expulsion; declared hypersensitivity to tamsulosin or corticosteroids; previous ureteral surgery.
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Deflazacort: 30 mg daily. <p>Treatment group 3</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily. • Deflazacort: 30 mg daily. <p>Control group</p> <ul style="list-style-type: none"> • Analgesics on demand. <p>All participants received first treatment with 500 mL saline and analgesic (diclofenac or tramadol).</p> <p>All participants were allowed to use symptomatic therapy with IM injections of diclofenac (on demand) and were instructed to drink a minimum of 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Analgesic consumption. • Safety. • Number of ureteroscopies.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Treatment on an "intention-to-treat" basis.</p> <p>Sample size calculated.</p>

Porpiglia 2006 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Not all participants received CT scan at the end of the trial period. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: small number (3) of participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Porpiglia 2009

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: April 2006 to September 2007. • Follow-up/Treatment duration: 10 days.
Participants	<ul style="list-style-type: none"> • Country: Italy. • Setting: single centre. • Patients with 5-10 mm distal ureteral stones, which were previously treated with 10 days of MET (tamsulosin 0.4 mg and deflazacort 30 mg daily). • Number: treatment group: 46; control group: 45. • Mean age \pm SD, years: treatment group: 51 \pm 13.9; control group: 46 \pm 14.6. • Sex, M/F: treatment group: 17/29; control group: 23/22. • Exclusion criteria: fever; analgesic non-responder renal colic; intolerance to tamsulosin and severe hydronephrosis on US; history of spontaneous stone expulsion; hypotension; previous ureteral surgery.

Porpiglia 2009 (Continued)

Interventions	Treatment group <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. Control group <ul style="list-style-type: none"> No treatment. <p>All participants were allowed to use therapy to alleviate symptoms, that is, IM injections with 75 mg diclofenac on demand, and were required to drink ≥ 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Number of episodes of colic. Analgesic consumption. Side effects. Changes in WBC count and creatinine.
Funding sources	None stated.
Declarations of interest	None.
Notes	Sample size calculated. Follow-up only at the end of the study (11th day).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.

Porpiglia 2009 (Continued)

Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.
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Rahim 2012

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: 24 November 2008 to 24 May 2009. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: Pakistan. • Setting: single centre. • Patients with 4-7 mm distal ureteral stones. • Number: treatment group: 45; control group: 45. • Mean age \pm SD, years: treatment group: 32.40 \pm 10.28; control group: 32.84 \pm 12.13. • Sex, M/F: treatment group: 32/13; control group: 31/14. • Exclusion criteria: UTI; severe hydronephrosis; pregnancy; ulcer disease; hypotension; patients taking calcium channel blockers; serum creatinine more than 2 mg/dL; multiple ureteral stones; bilateral distal ureteral stones; solitary kidney; ureteral stricture; patients desiring immediate stone retrieval.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. • Diclofenac sodium 50 mg tablets twice daily. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac sodium 50 mg tablets twice daily. <p>Follow-up weekly with US.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion: yes/no. • Stone expulsion time. • Stone size. • Analgesic consumption (not mentioned in Results section).
Funding sources	None stated.
Declarations of interest	None stated.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random number table." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement.

Rahim 2012 (Continued)

		Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Total dosage of diclofenac used was not described in Results section, although it was mentioned as an outcome measurement in the Methods section. Owing to this inconsistency in describing outcome measurements, this type of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Sayed 2008

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: October 2005 and July 2006. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Egypt. • Setting: single centre. • Patients aged 18-62 years who had a unilateral distal ureteral stone (5-10 mm); evaluated by KUB, US, and IV urography. • Number: treatment group: 45; control group: 45. • Mean age \pm SD, years: treatment group: 39.39 \pm 10.6; control group: 37.19 \pm 9.8. • Sex, M/F: treatment group: 34/11; control group: 35/10. • Exclusion criteria: UTI; severe hydronephrosis; multiple stones; pregnancy; lactation; hypotension; ureteral stricture or a history of spontaneous stone passage; concomitant treatment with alphalytic drugs; beta-blockers or calcium antagonists; desire of patient for immediate stone removal.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. • Standard therapy. <p>Control group</p> <ul style="list-style-type: none"> • Standard therapy: hydration (at least 2 L water/d) and injection of 100 mg of diclofenac on demand.
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate.

Sayed 2008 (Continued)

- Stone expulsion time.
- Pain episodes.
- Total analgesic dosage.

Funding sources	None stated.
Declarations of interest	None stated.
Notes	Every week, a clinical examination was performed and KUB X-rays and abdominal US were obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, risk of allocation concealment was considered to be unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Sen 2017

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: December 2013 to July 2015. • Follow-up/Treatment duration: 3 weeks.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre.

Sen 2017 (Continued)

- Patients with distal ureteral stones that were radio-opaque and ≤ 10 mm.
- Number: treatment group 1: 25; treatment group 2: 22; control group: 19.
- Mean age \pm SD, years: treatment group 1: 30 ± 7.6 ; treatment group 2: 37.9 ± 11.5 ; control group: 33 ± 11.3 .
- Sex, M/F: treatment group 1: 18/7; treatment group 2: 17/5; control group: 11/8.
- Exclusion criteria: hypersensitivity to agents used; advanced hydronephrosis; persistent pain despite proper and adequate analgesic use; urinary tract infection; low blood pressure.

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Doxazosin 4 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> • Doxazosin 8 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • All participants received diclofenac 100 mg orally and daily hydration.
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Number of pain episodes. • Quantity of analgesics.
Funding sources	None stated.
Declarations of interest	None.
Notes	Weekly follow-up urine analysis and radiological assessment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the MedCalc statistical software." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: No participants lost to follow-up; therefore risk of attrition bias was considered to be low.

Sen 2017 (Continued)

Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Stone clearance rate and stone clearance time were not predefined explicitly in the Methods section. Owing to this inconsistency in describing outcome measurements, this type of reporting bias was considered to be unclear.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Sun 2009

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: March 2006 to January 2007. • Follow-up/Treatment duration: not described.
Participants	<ul style="list-style-type: none"> • Country: China. • Setting: single centre. • Patients between 18-65 years with unilateral distal ureteral stones, diagnosed by US and KUB, and urogram when necessary. • Number: treatment group: 30; control group: 30. • Mean age \pm SD, years: treatment group: 38.2 ± 12.6; control group: 37.8 ± 10.2. • Sex, M/F: treatment group: 26/4; control group: 24/6. • Exclusion criteria: multiple stones; severe incarcerated stones; history of distal ureteral surgery or spontaneous stone expulsion; renal colic > 24 hours in duration; UTI; severe hydronephrosis; voiding dysfunction; hypotension; cardiovascular and cerebrovascular diseases; hepatic and kidney dysfunction; pregnancy; diabetes and ulcer disease; history of hypersensitivity to naftopidil; concomitant treatment with cardiovascular drugs, alpha-blocker, or calcium channel blocker.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Naftopidil 50 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> • Watchful waiting. <p>All participants were instructed to drink a minimum of 2 L water daily. An indomethacin suppository was used to control acute episodes of ureteral colic, if present.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion time. • Stone expulsion rate. • Adverse events of medication. • Stone size. • Number of hospitalisations. • Number of ureteral colics.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Naftopidil = selective alpha-1D.

Sun 2009 (Continued)

Ultrasonography and KUB were performed on days 7 and 14.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	High risk	No quotes available. Comment: Number of pain episodes and requirement for pain medication were not reported explicitly. Owing to this inconsistency in describing outcome measurements, risk of this type of reporting bias was considered to be high.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Sur 2015

Methods	<ul style="list-style-type: none"> • Study design: DB placebo-controlled RCT. • Study duration: July 2010 and July 2012. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: USA. • Setting: multi-centre. • Patients ≥ 18 years with a unilateral calculus ≥ 4 mm and ≤ 10 mm at any location of the ureter visible within 7 days of study enrolment on kidney/ureter/bladder radiograph (KUB) and/or non-contrast helical computed tomography (CT). • Number: treatment group: 122; placebo group: 124. • Mean age \pm SD, years: treatment group: 47 ± 13; placebo group: 47 ± 15. • Sex, M/F: treatment group: 72/43; placebo group: 80/37.

Sur 2015 (Continued)

- Exclusion criteria: multiple ureteral calculi; a solitary kidney; refractory renal colic (renal colic or nausea/emesis that could not be well controlled with outpatient medications); a non-opaque calculus; severe hydronephrosis.

Interventions

Treatment group

- Silodosin 8 mg daily.

Placebo group

- Placebo drug.

All participants received pain medication (oxycodone 5 mg). Other medication that would not confound study results was permitted and documented.

Outcomes

Primary outcome variables

- Stone expulsion rate.

Secondary outcome variables

- Stone expulsion time.
- Need for ED visits or hospital admissions.
- Adverse events of medication.
- Need for surgical intervention.
- Need for outpatient narcotic use for pain relief.
- Incidence and severity of pain.

Funding sources

Actavis Inc. supported the study.

Declarations of interest

None stated.

Notes

Power calculation, intention-to-treat-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... using a randomization schedule prepared by a nonstudy statistician." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Each kit had a unique sequential number." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigator, patient, and study team were blinded to treatment assignment throughout the study." Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No quotes available. Comment: Personnel responsible for outcome assessments were blinded; therefore risk of detection bias was considered to be low.

Sur 2015 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: Numbers of participants lost to follow-up in the different study groups were equally distributed; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Taghavi 2005

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: October 2003 to February 2004. • Follow-up/Treatment duration: 20 days.
Participants	<ul style="list-style-type: none"> • Country: Iran. • Setting: single centre. • Patients suffered from juxtavesical stone < 1 cm. • Number: treatment group 1: 20; treatment group 2: 20; control group: 24. • Mean age: 38 years. • Sex, M/F:35/29. • Exclusion criteria: NS.
Interventions	Treatment group 1 <ul style="list-style-type: none"> • Tamsulosin 0.4 mg. Treatment group 2 <ul style="list-style-type: none"> • Nifedipine 20 mg. Control group <ul style="list-style-type: none"> • No treatment.
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Conference abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Taghavi 2005 (Continued)

Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No quotes available. Comment: Loss to follow-up was not described; therefore risk of attrition bias was considered to be unclear.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of reporting bias was considered unclear.
Other bias	Unclear risk	No quotes available. Comment: Owing to insufficient information to permit judgement, risk of other sources of bias was considered to be unclear.

Vincendeau 2010

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT. • Study duration: 1 February 2002 to 8 December 2006. • Follow-up/Treatment duration: 6 weeks.
Participants	<ul style="list-style-type: none"> • Country: France. • Setting: multi-centre. • Patients > 18 years hospitalised in emergency wards for acute renal colic and having a radio-opaque distal ureteral stone between 2 and 7 mm. • Number: treatment group: 66; control group: 63. • Mean age \pm SD, years: treatment group: 38.9 \pm 13.4; control group: 39.0 \pm 11.4. • Sex, M/F: treatment group: 43/18; control group: 52/9. • Exclusion criteria: pregnant or breastfeeding women; receiving alpha-/beta-blockers; transient hypotension; liver impairment; requiring surgical procedure because of infection or continuation of pain after medical treatment; spontaneous passage before randomisation.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg daily for 42 days or until stone expulsion. <p>Control group</p>

Vincendeau 2010 (Continued)

- Matching placebo for 42 days or until stone expulsion.

Both groups received ketoprofen 50 mg, 3 capsules daily, and phloroglucinol 80 mg, 6 tablets daily, for 5 days.

All participants were told to drink at least 2 L water daily and to filter urine.

Outcomes	<ul style="list-style-type: none"> • Time to stone expulsion. • Rate of stone expulsion. • Number of pain relapses. • Dosage of pain medication. • Adverse events.
Funding sources	Financed by the French Ministry of Health and Yamanouchi Pharmaceutical Co Ltd.
Declarations of interest	Dr. Vincendeau is an investigator for Astellas Pharma Inc, AstraZeneca, Beckman-Coulter/Hybritech Inc, and Pfizer Incorporated.
Notes	<p>Follow-up of 42 days.</p> <p>Evaluation with X-ray and US on days 1, 14, 28, and 42. Telephone contact on days 21 and 35.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Randomization was centrally performed, concealed, and stratified by center in blocks of 4 according to a computer generated random number table."</p> <p>Comment: This method of random sequence generation was considered to have low risk of bias.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "... sequentially numbered boxes containing the whole treatment for each patient following the order of the randomization list."</p> <p>Comment: This method of allocation concealment was considered to have low risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "All patients, health medical and nursing staffs, and pharmacists remained masked throughout the study period."</p> <p>Comment: Double-blinding was performed; therefore risk of performance bias was considered to be low.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>No quotes available.</p> <p>Comment: Personnel responsible for outcome assessments were blinded; therefore risk of detection bias was considered to be low.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>No quotes available.</p> <p>Comment: missing outcome data balanced in numbers across both groups, with similar reasons for missing data across groups; therefore risk of attrition bias was considered to be low.</p>
Selective reporting (reporting bias)	Low risk	<p>No quotes available. Expected outcomes were reported according to objectives.</p> <p>Comment: Risk of reporting bias was therefore considered to be low.</p>

Vincendeau 2010 (Continued)

Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.
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Wang 2008a

Methods	<ul style="list-style-type: none"> Study design: RCT. Study duration: May 2005 to December 2006. Follow-up/Treatment duration: 2 weeks.
Participants	<ul style="list-style-type: none"> Country: Taiwan. Setting: single centre. Patients with radio-opaque lower ureteral stones. Number: treatment group 1: 32; treatment group 2: 32; control group: 31. Mean age \pm SD, years: treatment group 1: 50.4 \pm 9.7; treatment group 2: 51.4 \pm 8.6; control group: 50.9 \pm 9.6. Sex, M/F: treatment group 1: 22/10; treatment group 2: 21/11; control group: 23/8. Exclusion criteria: UTI; high-grade hydronephrosis; diabetes; ulcers; history of hypersensitivity to 1-blockers; pregnant women; history of spontaneous stone expulsion; hypotension; systolic blood pressure 110 mm Hg; underwent previous ureteral surgery.
Interventions	<ul style="list-style-type: none"> Treatment group 1 (tamsulosin 0.4 mg) Treatment group 2 (terazosin 2 mg) Control group <p>All participants were prescribed ketorolac 10 mg, 3 times/d, allowed to use sublingual buprenorphine 0.3 mg as needed, and were required to drink a minimum of 2 L water/d.</p>
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Number of episodes of colic. Lower urinary tract symptoms (frequency, residual urine, difficulty, urine retention, and tenesmus). Amount of analgesic consumed. Adverse events.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Follow-up with KUB and abdominal US.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... randomly divided into three groups using the statistical software programs Plus 1.0 and Plus 2.10." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement.

Wang 2008a (Continued)

		Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Ye 2017

Methods	<ul style="list-style-type: none"> • Study design: double-blind placebo-controlled RCT. • Study duration: 1 September 2011 and 31 August 2013. • Follow-up/Treatment duration: 28 days.
Participants	<ul style="list-style-type: none"> • Country: China. • Setting: multi-centre. • Inclusion criteria: adults, 18 to 60 years; emergency admission for renal colic; presence of a single ureteral stone confirmed by plain abdominal radiography (kidney–ureters–bladder), urinary ultrasonography, and/or non-contrast computed tomography (CT); a stone in the distal ureter, with a dimension of 4–7 mm; and a unilateral presentation. • Number: treatment group: 1642; placebo group: 1654. • Mean age ± SD, years: treatment group: 40.1 ± 11.6, placebo group: 40.7 ± 12.3. • Sex, M/F: treatment group: 556/1086; placebo group: 605/1049. • Exclusion criteria: fever; urinary tract infections; severe hydronephrosis; renal insufficiency, defined by an estimated glomerular filtration rate < 60 mL/min per 1.73 m²; abnormal anatomy, such as a solitary kidney, a horseshoe kidney, or a duplex urinary system; urethrostenosis; history of ureter strictures; diabetes mellitus; hypotension (systolic blood pressure < 100 mm Hg); known or suspected pregnancy; current use of a-adrenoceptor antagonists or corticosteroids; previous history of ipsilateral ureteral surgery, spontaneous stone expulsion, or known or suspected allergy to study medications.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg (2 capsules of 0.2 mg daily). <p>Placebo group</p> <ul style="list-style-type: none"> • All participants received 50 mg sodium diclofenac suppository on demand.

Ye 2017 (Continued)

Outcomes	Primary endpoints <ul style="list-style-type: none"> Stone expulsion rate, defined as stone expulsion, confirmed by negative findings on CT. Secondary endpoints <ul style="list-style-type: none"> Time to stone expulsion. Rate of use of pain relief therapy during treatment. Average analgesic consumption for recurrent renal colic. Incidence of adverse events.
Funding sources	Supported by health industry special scientific research projects, Ministry of Health of China (201002010). Astellas Pharma supported this study and was involved in preparation of the manuscript. No financial disclosures.
Declarations of interest	None.
Notes	Weekly follow-up with CT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization and double blinding were performed according to the randomization sequence, which was produced with a computer-generated program." Comment: This method of random sequence generation was considered to have low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered study e-packs were securely stored at each study center using a password-protected computer database and were known only to the trial designer and statistician." Comment: This method of allocation concealment was considered to have low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigator, participants, care providers, and those assessing outcomes were blinded to treatment assignment throughout the trial, as the randomization list was generated by an independent statistician and was not available until the study analysis." Comment: double-blind; therefore low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigator, participants, care providers, and those assessing outcomes were blinded to treatment assignment throughout the trial, as the randomization list was generated by an independent statistician and was not available until the study analysis." Comment: blinding of outcome assessment; therefore risk of detection bias was considered to be low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Figure 1 shows the trial profile with a detailed schedule of participant follow-up including information regarding loss to follow-up, withdrawal percentage, etc. Intention-to-treat analysis was used. Comment: Detailed information on participant follow-up was available; risk of attrition bias was considered to be low.

Ye 2017 (Continued)

Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Yencilek 2010

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: December 2004 and November 2008. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Patients with radio-opaque proximal ureteral stones ≤ 10 mm; radiological evaluation with X-ray, US, and in some cases NCCT. • Number: treatment group: 42; control group: 50. • Mean age \pm SD, years: treatment group: 34.9 ± 11.8; control group: 33.5 ± 10.1. • Sex, M/F: treatment group: 24/18; control group: 30/20. • Exclusion criteria: severe hydronephrosis; solitary kidney; extra stone in the upper urinary system; previous surgical history; diabetes; hypertension; pregnancy; reduced kidney function.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily. • Hyoscine-N-butylbromide 10 mg 3 times daily. <p>Control group/group 1</p> <ul style="list-style-type: none"> • Hyoscine-N-butylbromide 10 mg 3 times daily. <p>All participants were instructed for adequate hydration.</p>
Outcomes	<ul style="list-style-type: none"> • Stone passage rate. • Mean stone expulsion time. • Mean VAS score. • Change in colic episodes. • Hospital re-admission rates for colicky pain attacks.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	<p>Follow-up of 4 weeks.</p> <p>Evaluation with X-ray, US, or NCCT when stone passage occurred.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Yencilek 2010 (Continued)

Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Yilmaz 2005

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: NS. • Follow-up/Treatment duration: 1 month.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: NS. • Patients, 18-65 years, with radio-opaque stones ≤ 10 mm located in the distal ureter; assessment by KUB and US before treatment. • Number: treatment group 1: 29; treatment group 2: 28; treatment group 3: 29; control group: 28. • Mean age \pm SD, years: treatment group 1: 40.62 ± 10.27; treatment group 2: 41.67 ± 11.41; treatment group 3: 42.13 ± 10.4; control group: 41.60 ± 12.01. • Sex, M/F: treatment group 1: 9/20; treatment group 2: 9/19; treatment group 3: 9/20; control group: 19/9. • Exclusion criteria: presence of UTI; radiolucency stones; severe hydronephrosis; diabetes; ulcer disease; hypotension; having calcium antagonist; history of distal ureter surgery.
Interventions	Treatment group 1 <ul style="list-style-type: none"> • Tamsulosin 0.4 mg once daily.

Yilmaz 2005 (Continued)

Treatment group 2

- Terazosin 5 mg once daily.

Treatment group 3

- Doxazosin 4 mg once daily.

Control group

- No treatment.

All participants were allowed to use symptomatic therapy with injections of 75 mg diclofenac on demand and were required to consume a minimum of 2 L of water daily.

Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Amount of analgesic compound. • Pain episodes.
Funding sources	None stated.
Declarations of interest	None stated.
Notes	Each participant was controlled with KUB and US every week.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias.

Yilmaz 2005 (Continued)

Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Yuksel 2015

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: March 2013 to May 2014. • Follow-up/Treatment duration: 21 days.
Participants	<ul style="list-style-type: none"> • Country: Turkey. • Setting: single centre. • Patients: detection of a distal ureteral stone 4-10 mm in diameter. • Number: treatment group: 35; control group: 35. • Mean age \pm SD, years: treatment group: 35.31 \pm 11.55; control group: 35.23 \pm 11.20. • Sex, M/F: treatment group: 20/15; control group: 19/35. • Exclusion criteria: younger than 18 or over 65 years of age; presence of multiple stones; grade 3 or 4 hydronephrosis; solitary or transplanted kidney; urinary tract infection; recurrent and persistent renal colic in reaction to analgesic administration; renal failure; allergic reaction to NSAID or alpha-blocker treatment; hypotension; current intake of alpha-blockers, CCBs, or steroids.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Silodosin 4 mg daily + diclofenac sodium on demand. <p>Control group</p> <ul style="list-style-type: none"> • Diclofenac sodium on demand. <p>Both groups were also advised to remain active and to drink at least 2 L of water daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Number of renal colic episodes. • Need for analgesics. • Stone size.
Funding sources	None stated.
Declarations of interest	None.
Notes	Follow-up weekly visits with X-ray or low-dose CT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No quotes available. Comment: randomisation stated but no information on method used was available; therefore selection bias was considered to have unclear risk of bias.
Allocation concealment (selection bias)	Unclear risk	No quotes available. Insufficient information to permit judgement. Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.

Yuksel 2015 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No quotes available. No blinding described. Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Unclear risk	No quotes available. Comment: Adverse effects were not described in the Results section, although they were stated as secondary outcomes in the Methods section; therefore risk of reporting bias was considered to be unclear.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Zehri 2010

Methods	<ul style="list-style-type: none"> • Study design: open-label RCT. • Study duration: 15 March 2007 to 15 September 2007. • Follow-up/Treatment duration: 4 weeks.
Participants	<ul style="list-style-type: none"> • Country: Pakistan. • Setting: single centre. • Patients with distal ureteral stones 4-7 mm, presenting to the ED or to the outpatient clinic; assessed with NCCT. • Number: treatment group: 33; control group: 32. • Mean age, years: treatment group: 32.63; control group: 33.62. • Sex, M/F: treatment group: 31/2; control group: 25/7. • Exclusion criteria: UTI; ureteral stricture; diabetes; ulcer disease; history of hypersensitivity to doxazosin; solitary kidney; severe hydronephrosis; SCr > 2 mg/dL; multiple ureteral stones; hypotension; pain not controlled on analgesics; pregnant.
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Doxazosin 2 mg 1 hour before sleep for a maximum of 28 days. <p>Control group</p> <ul style="list-style-type: none"> • No treatment. <p>Both groups received 50 mg diclofenac twice daily for a maximum of 10 days and were allowed to drink 2 L of fluids daily.</p>
Outcomes	<ul style="list-style-type: none"> • Stone expulsion rate. • Stone expulsion time. • Quantity of analgesics used.

Zehri 2010 (Continued)

- Need for hospitalisation or endoscopic procedures or both.
- Side effects.

Funding sources	None stated.
Declarations of interest	None stated.
Notes	Weekly follow-up with KUB or US. Sample size was calculated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was done by assigning consecutive patients to alternate groups." Comment: This method of random sequence generation was considered to have high risk of bias.
Allocation concealment (selection bias)	High risk	No quotes available. Comment: The type of allocation concealment used in this study was considered to have high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label." No blinding performed. Comment: Risk of performance bias was considered to be high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: one exclusion; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

Zhou 2011

Methods	<ul style="list-style-type: none"> • Study design: RCT. • Study duration: December 2008 to September 2010. • Follow-up/Treatment duration: 2 weeks.
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Zhou 2011 (Continued)

Participants	<ul style="list-style-type: none"> Country: China. Setting: single centre. Patients with a distal ureteral stone (< 10 to > 4 mm). Number: treatment group 1: 43; treatment group 2: 45; control group: 43. Mean age \pm SD, years: treatment group 1: 33.73 \pm 8.84; treatment group 2: 34.42 \pm 8.64; control group: 34.79 \pm 9.63. Sex, M/F: treatment group 1: 25/18; treatment group 2: 27/18; control group: 27/16. Exclusion criteria: multiple stones; severe incarcerated stones; history of distal ureteral surgery; history of spontaneous stone expulsion; renal colic for longer than 24 hours; urinary tract infection; severe hydronephrosis; voiding dysfunction; hypotension; cardiovascular and cerebrovascular diseases; hepatic and renal dysfunction; pregnancy and diabetes; history of hypersensitivity to naftopidil; receiving treatment with cardiovascular drugs, alpha-receptor antagonists, or calcium antagonists. 	
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Naftopidil 10 mg once daily. <p>Treatment group 2</p> <ul style="list-style-type: none"> Tamsulosin 0.4 mg once daily. <p>Control group</p> <ul style="list-style-type: none"> Watchful waiting. <p>Both groups were also advised to drink at least 2 L of fluids daily. An indomethacin suppository was recommended for routine use during pain episodes.</p>	
Outcomes	<ul style="list-style-type: none"> Stone expulsion rate. Stone expulsion time. Number of pain episodes. Requirements for pain medication. Side effects of naftopidil. 	
Funding sources	None stated.	
Declarations of interest	None.	
Notes	Follow-up weekly with KUB and ultrasonography.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>No quotes available.</p> <p>Comment: randomisation stated but no information on method used was available; therefore risk of selection bias was considered to be unclear.</p>
Allocation concealment (selection bias)	Unclear risk	<p>No quotes available. Insufficient information to permit judgement.</p> <p>Comment: Owing to insufficient information, allocation concealment was considered to have unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>No quotes available. No blinding described.</p> <p>Comment: Owing to insufficient information, risk of performance bias was considered to be unclear.</p>

Zhou 2011 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No quotes available. No blinding of outcome assessments described. Comment: Owing to insufficient information, risk of detection bias was considered to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No quotes available. Comment: no participants lost to follow-up; therefore risk of attrition bias was considered to be low.
Selective reporting (reporting bias)	Low risk	No quotes available. Expected outcomes were reported according to objectives. Comment: Risk of reporting bias was therefore considered to be low.
Other bias	Low risk	No quotes available. Study appears to be free of other sources of bias. Comment: No other sources of bias could be found; therefore risk of other bias was considered to be low.

AKI: acute kidney injury; CCB: calcium channel blocker; CKD: chronic kidney disease; CT: computed tomography; DB: double-blind; ED: emergency department; eGFR: estimated glomerular filtration rate; ESWL: extracorporeal shockwave lithotripsy; EuroQOL: EuroQOL Group quality of life questionnaire; GFR: glomerular filtration rate; HRQOL: health-related quality of life; HTA: health technology assessment; HU: Hounsfield unit; IM: intramuscular; IQR: interquartile ratio; IV: intravenous; IVU: Intravenous urography; KUB: kidney, ureter, and bladder plain x-ray; MET: medical expulsive therapy; NCCT: non-contrast computed tomography; NHS: National Health Service; NIHR: National Institute for Health Research; NS: not stated; NSAID: non-steroidal anti-inflammatory drug; PDE5: phosphodiesterase type 5; QALY: quality-adjusted life-year; QOL: quality of life; RCT: randomised controlled trial; SCr: serum creatinine; SD: standard deviation; SWL: shockwave lithotripsy; US: ultrasound; UTI: urinary tract infection; VAS: visual analogue scale; WBC: white blood cell.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agarwal 2009	MET adjunct therapy to ESWL.
Aravinthan 2012	Stones larger than 10 mm were included, and data could not be separated for adequate analysis of stones measuring 10 mm or less.
Avdoshin 2005	Stones larger than 10 mm were included, and separate data were not available for stones measuring 10 mm or less.
Aydogdu 2009	Participants were children.
Bak 2007	No extracted data were available.
Bhat 2015	Prospective study, but unclear whether this study was randomised.
Borghi 1994	Intervention was calcium channel blocker.
Brausi 2015	No randomisation was performed.
Chau 2011	Patients with pyelonephritis were included.
Cooper 2000	Intervention was calcium channel blocker.
Cuni 2013	Use of Rowatinex/Terpenes vs tamsulosin without control or placebo group.

Study	Reason for exclusion
Damiano 2008	Participants were patients who had undergone ureteral stent positioning.
Deliveliotis 2006	Participants were patients with stone-related hydronephrosis who had opted for conservative management with insertion of a double-J ureteral stent.
Dellabella 2003	Stones larger than 10 mm were included, and separate data were not available for stones measuring 10 mm or less.
Dellabella 2005	Stones larger than 10 mm were included, and separate data were not available for stones measuring 10 mm or less.
Dellabella 2005a	The intervention comprised corticosteroids added to 1 of 2 tamsulosin groups.
Gandhi 2013	Stones larger than 10 mm were included, and separate data were not available for stones measuring 10 mm or less.
Gupta 2013	Tamsulosin vs silodosin. No placebo or control group available for comparison.
Gupta Shyam 2014	Tamsulosin vs herbal preparation. No placebo or control group available for comparison.
Gurbuz 2011	Hyoscine-N-butylbromide (antispasmodic drug) vs alfuzosin vs doxazosin vs terazosin. HBB was not given to alpha-blocker groups. No placebo or control group available for comparison.
Haxhiu 2014	Unclear Results section. Data not interpretable.
Hwang 2012	Retrospective study.
Imperatore 2014	Tamsulosin vs silodosin. No placebo or control group available for comparison.
ISRCTN24675122	Study closed in January 2011 owing to insufficient recruitment.
Itano 2012	Retrospective study.
Jayant 2014	Tamsulosin vs tamsulosin and tadalafil. No placebo or control group available for comparison.
John 2010	Participants were patients with large renal or ureteral calculi who underwent ureteroscopic laser lithotripsy.
Khawaja 2005	Patients with multiple stones were included.
Kumar 2014	Tamsulosin vs tamsulosin and tadalafil. No placebo or control group available for comparison.
Kumar 2015	Tamsulosin and prednisolone vs naftopidil and prednisolone vs watchful waiting (no prednisolone). Therapy groups cannot be compared with watchful waiting group because prednisolone was used by treatment groups. Every positive effect reported in the therapy group could be due to use of prednisolone instead of the alpha-blocker.
Loftus 2015	Retrospective study.
Lu 2012	Naftopidil vs naftopidil and tolterodine vs tolterodine. No placebo or control group available for comparison.
Mohseni 2006	Stones larger than 10 mm were included, and separate data were not available for stones measuring 10 mm or less.
Moon 2015	Retrospective study.

Study	Reason for exclusion
Morozumi 2013	Naftopidil vs buscopan group. No placebo or control group available for comparison.
Multescu 2014	Retrospective study. Not an RCT.
Nasim 2014	Retrospective study.
Ohgaki 2010	Data on primary and secondary outcomes not available.
Porpiglia 2000	Intervention was calcium channel blocker.
Ramesh 2015	No information on inclusion and exclusion criteria available. Stones measuring > 7 mm were included; maximum diameter was unknown.
Reddy 2016	Study method is cohort; not an RCT.
Resim 2005	Stones larger than 10 mm were included; separate data were not available for stones measuring 10 mm or less.
Resorlu 2011	Investigators included no control group.
Salem 2015	Silodosin vs tamsulosin. No placebo or control group was available for comparison.
Sameer 2014	Children were included in the study (8 years old).
Shabana 2015	Tamsulosin vs alfuzosin. No placebo or control group was available for comparison.
Shah 2013	"Random base"; not an RCT.
Skrekas 2003	Intervention was calcium channel blocker.
Su 2016	Data were not consistent throughout the article. Participant numbers were different in tables as compared with the flow chart and text.
Sumer 2012	Primary outcome was resolution of colicky pain. Stone clearance rate was not reported.
Tchey 2011	Retrospective study.
Tszuka 2011	Naftopidil vs silodosin. No placebo or control group available for comparison.
Vavassori 2012	No randomisation performed.
Wang 2009c	Patients underwent ESWL before study entry.

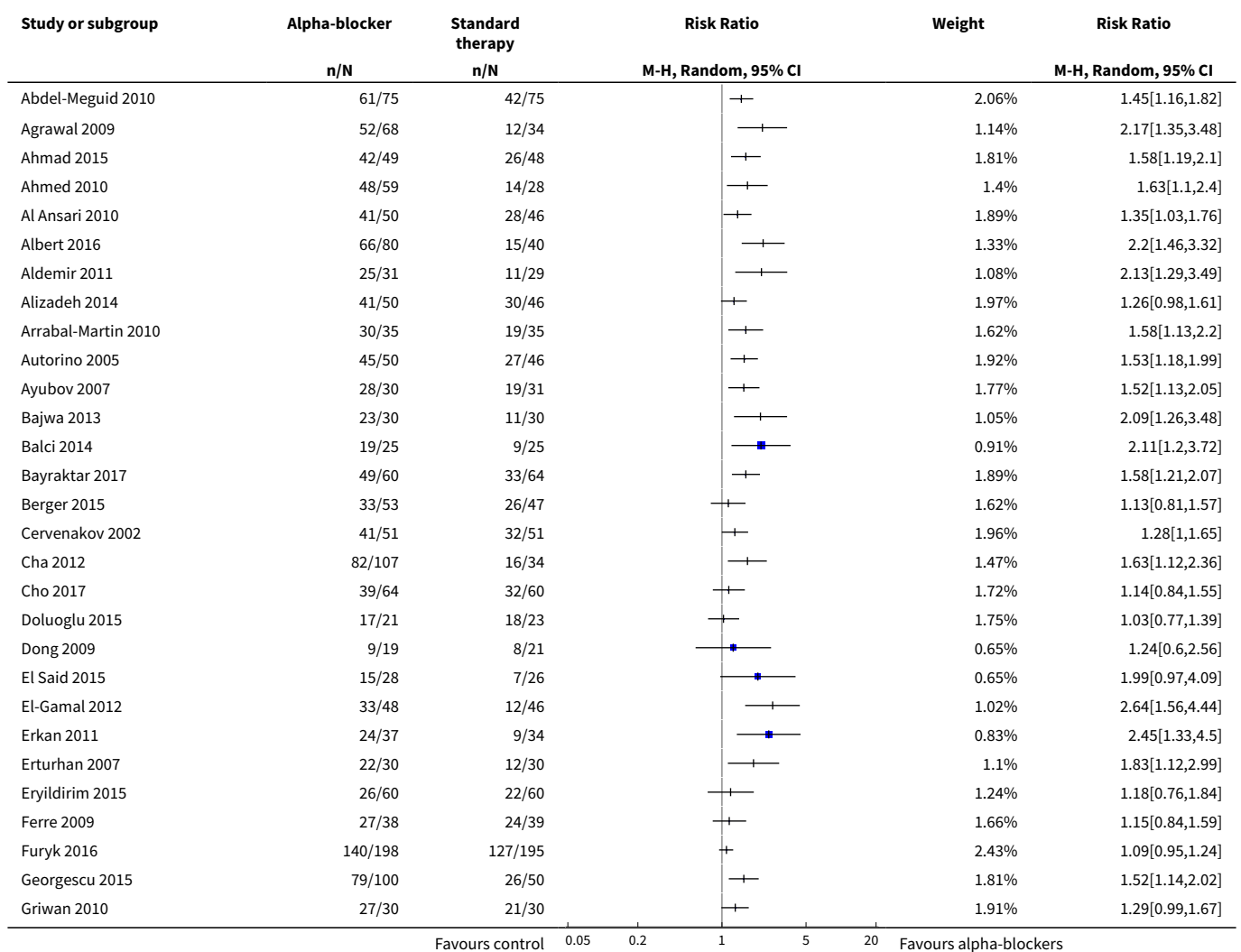
ESWL: extracorporeal shockwave lithotripsy; HBB: hyoscine-N-butylbromide; MET: medical expulsive therapy; RCT: randomised controlled trial.

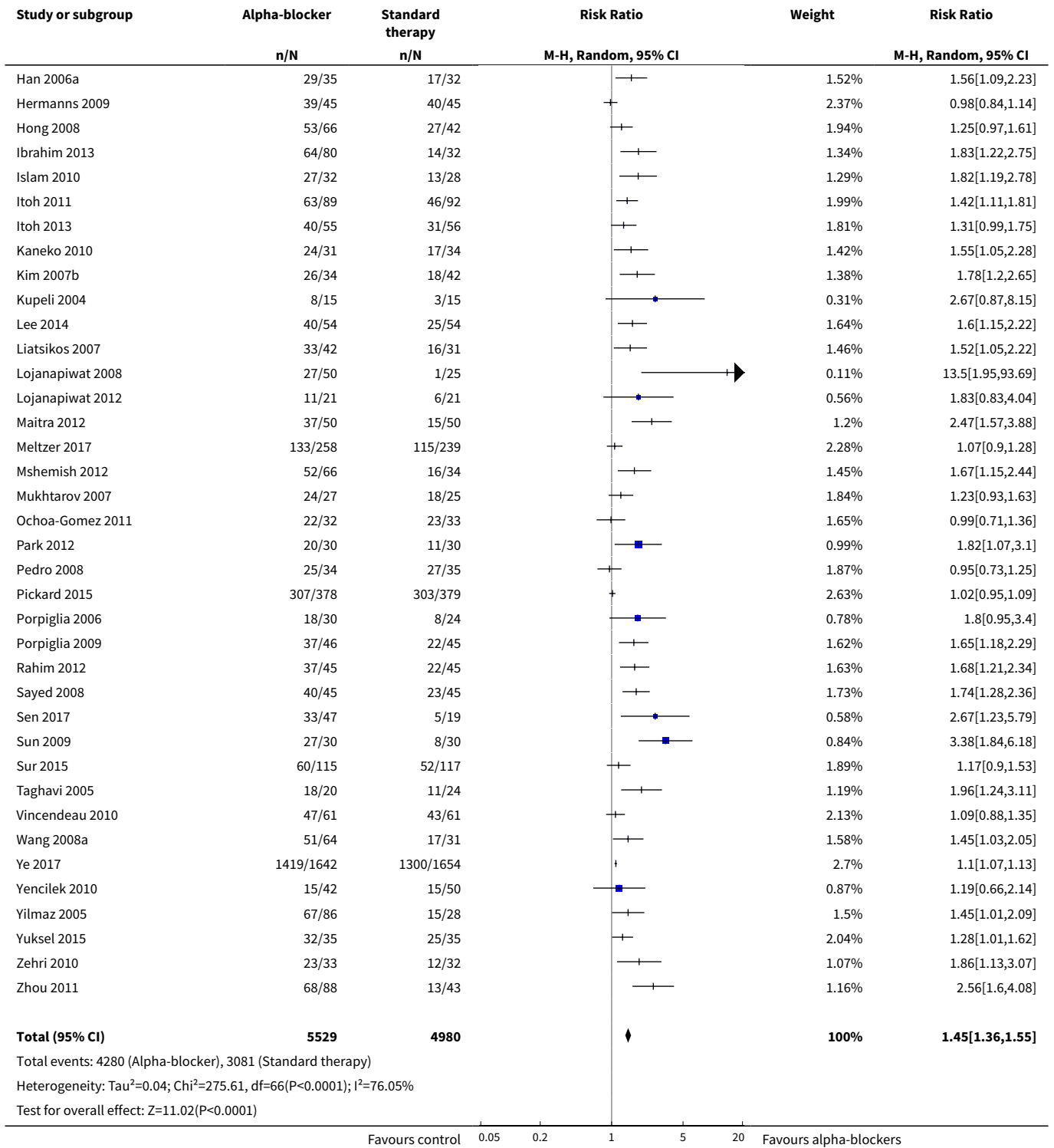
DATA AND ANALYSES

Comparison 1. Alpha-blocker versus standard therapy or placebo

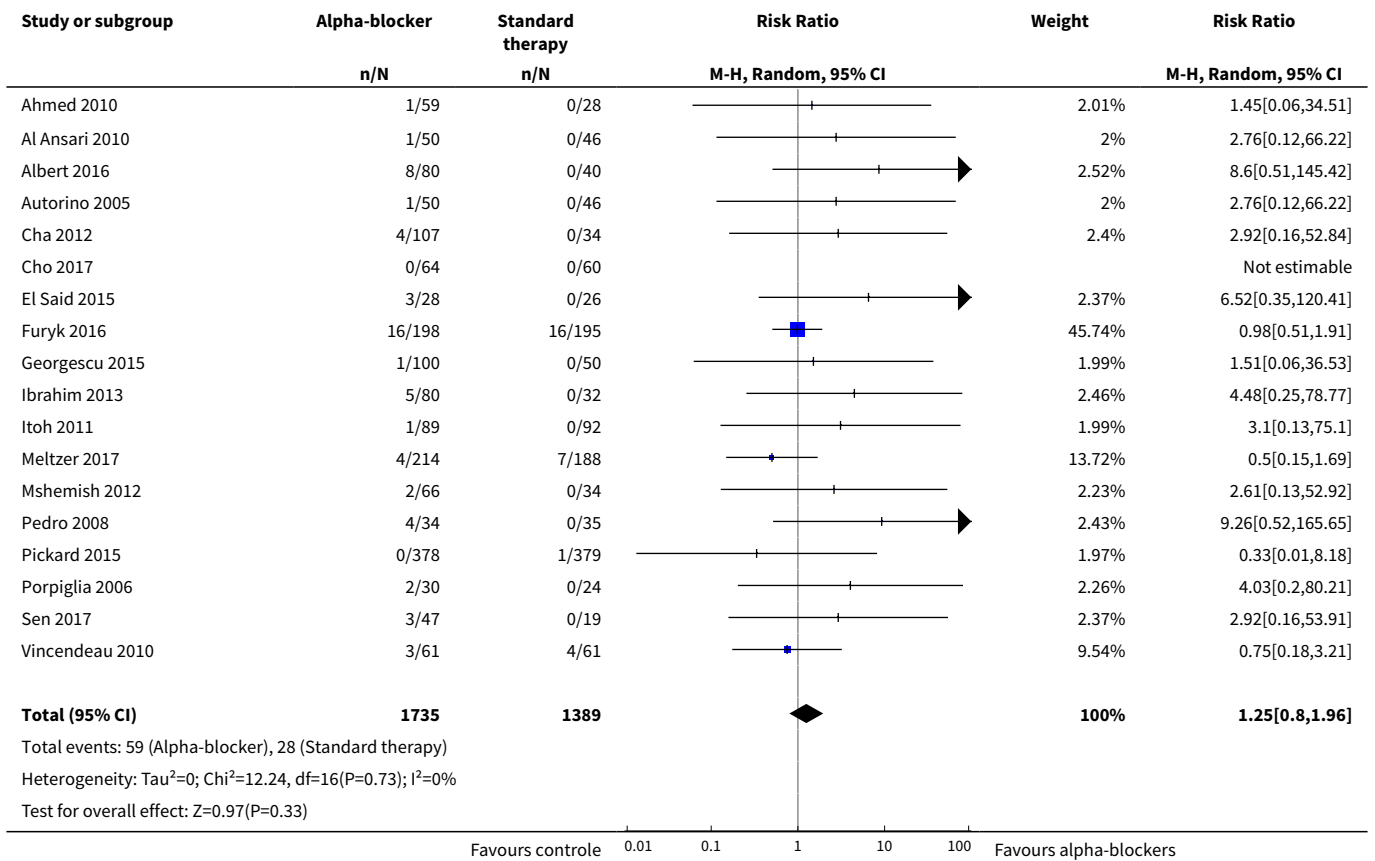
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	67	10509	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.36, 1.55]
2 Major adverse events	18	3124	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.80, 1.96]
3 Stone expulsion time	37	6031	Mean Difference (IV, Random, 95% CI)	-3.40 [-4.17, -2.63]
4 Pain episodes	15	1363	Mean Difference (IV, Random, 95% CI)	-0.66 [-0.91, -0.42]
5 Dose of diclofenac	14	4373	Mean Difference (IV, Random, 95% CI)	-82.41 [-122.51, -42.31]
6 Hospitalisation	13	1876	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
7 Surgical intervention	19	3292	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.02]

Analysis 1.1. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 1 Stone clearance.

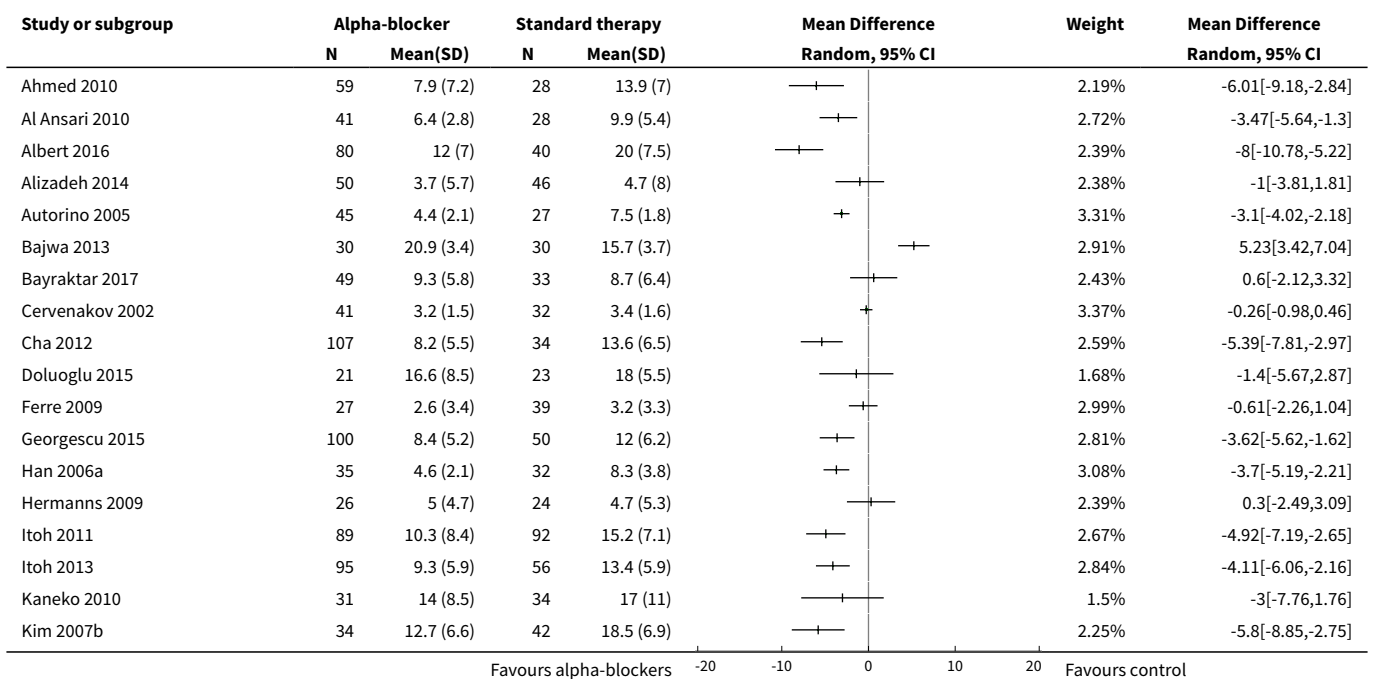


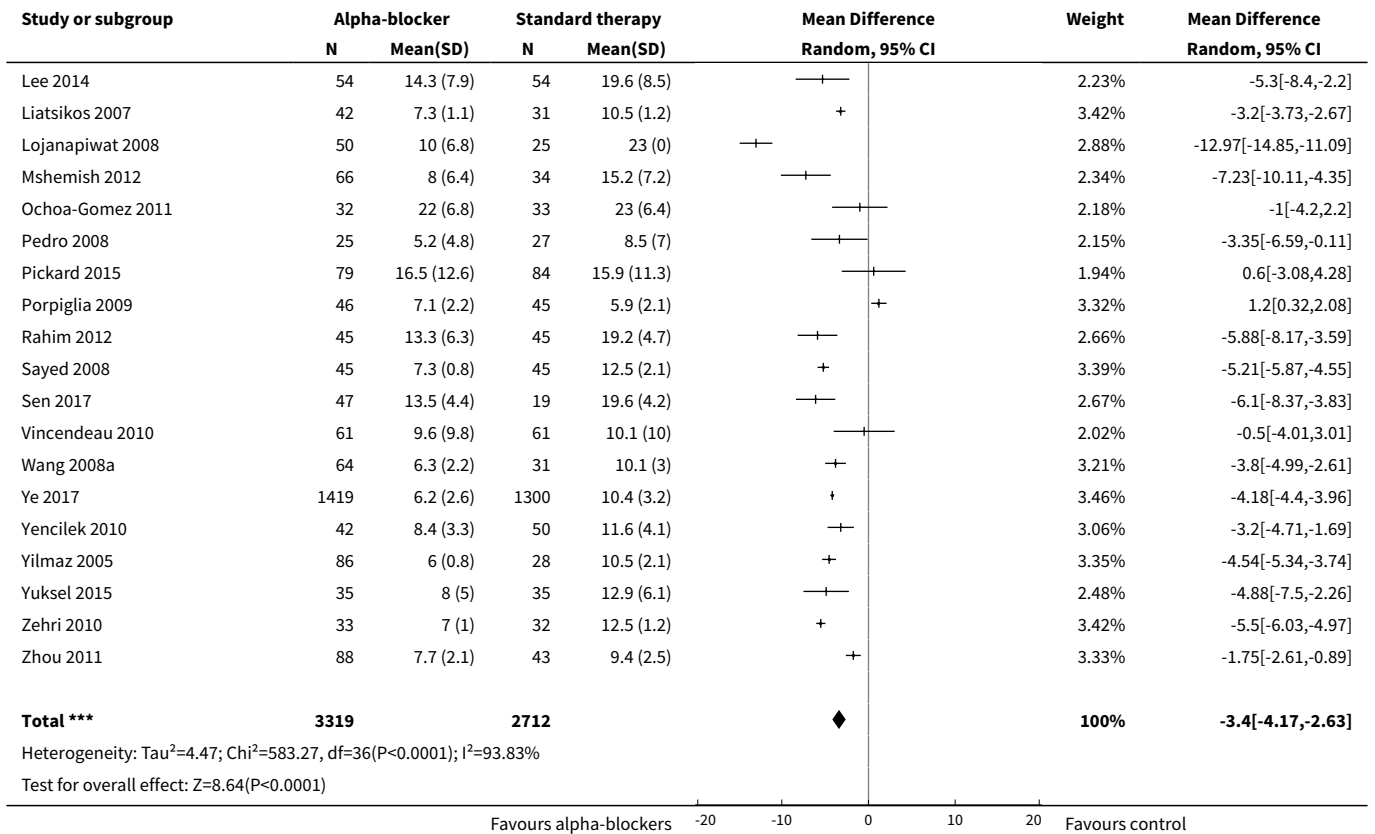


Analysis 1.2. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 2 Major adverse events.

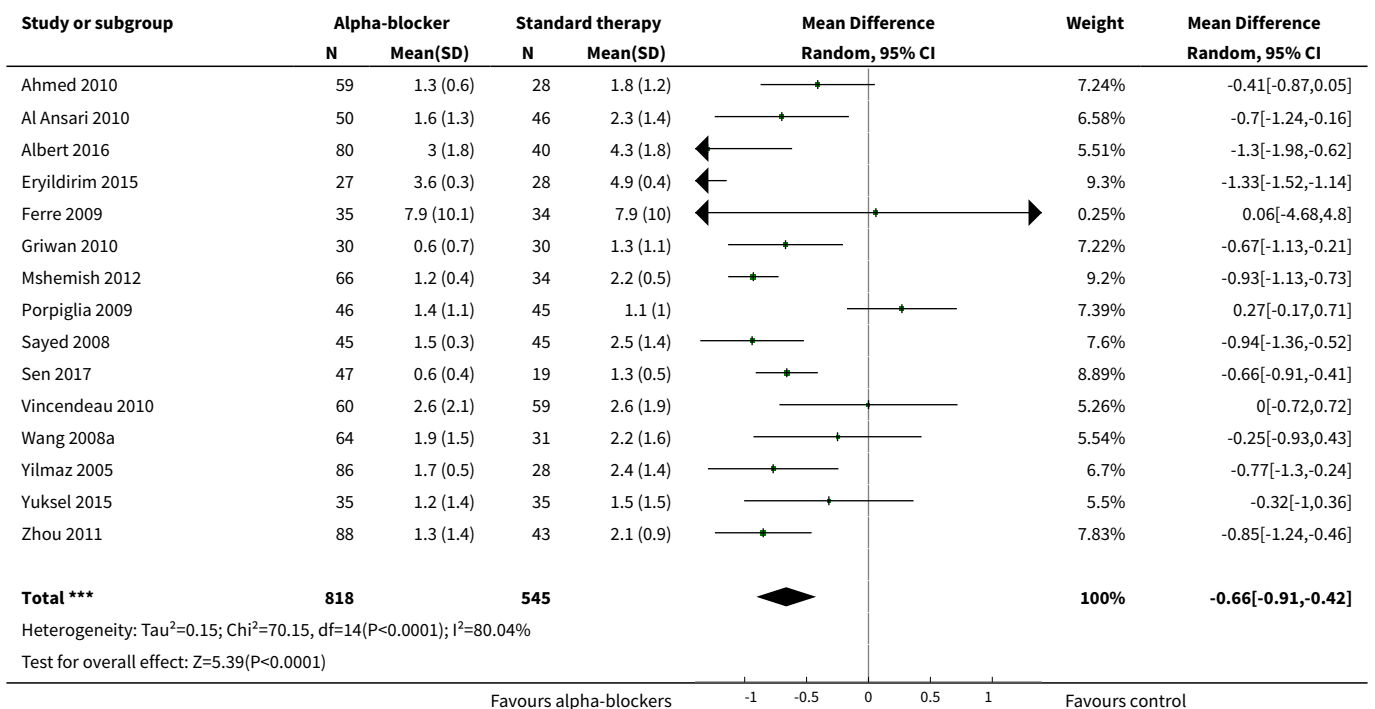


Analysis 1.3. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 3 Stone expulsion time.

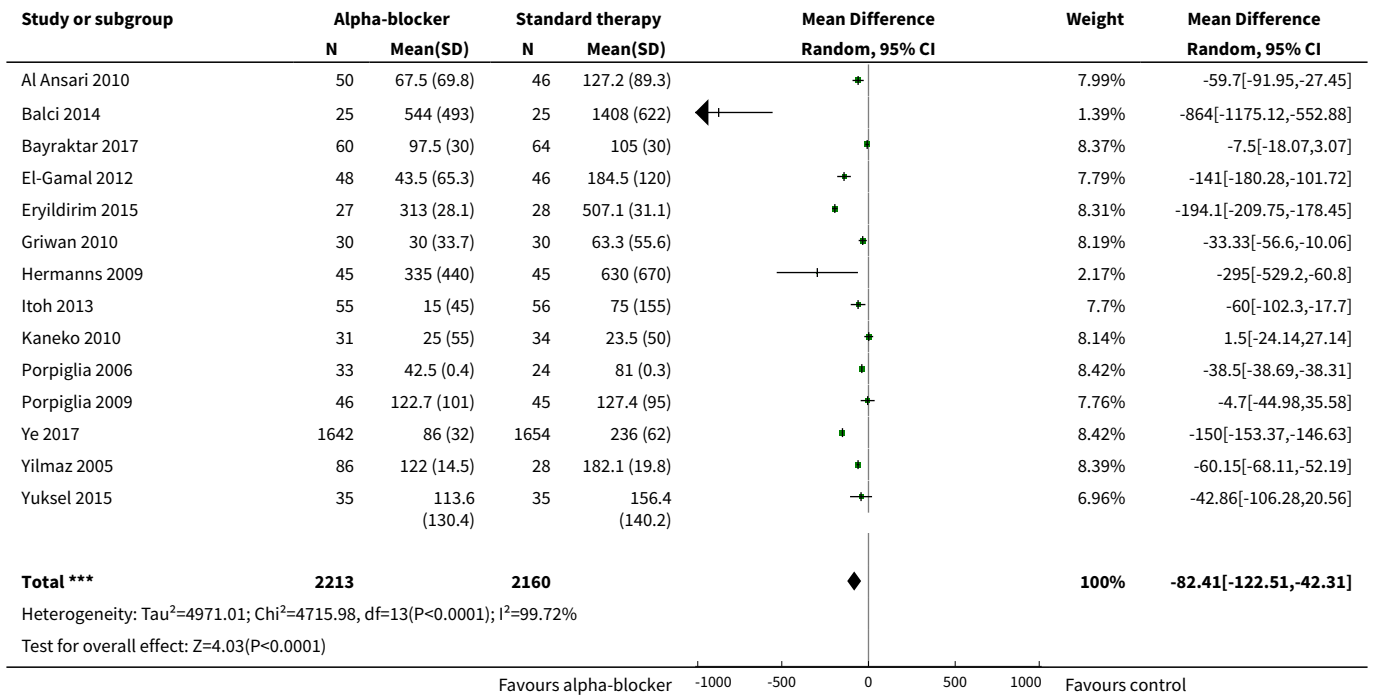




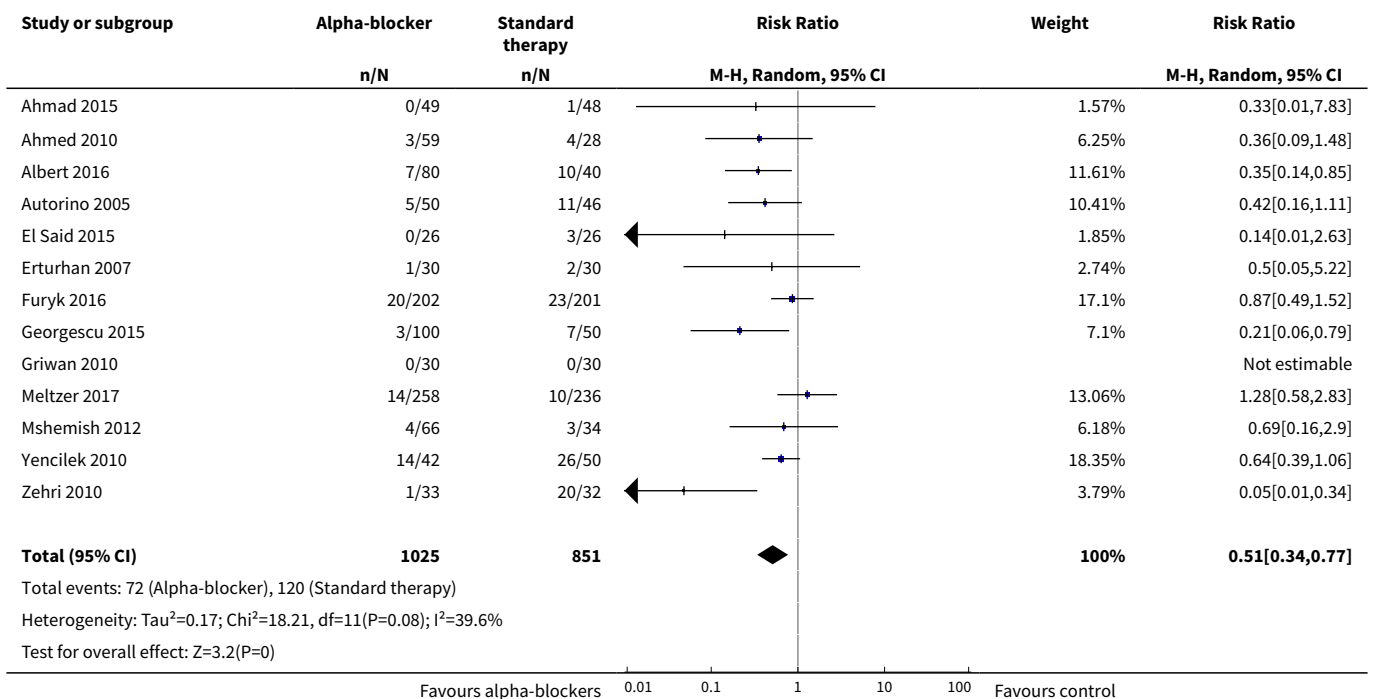
Analysis 1.4. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 4 Pain episodes.



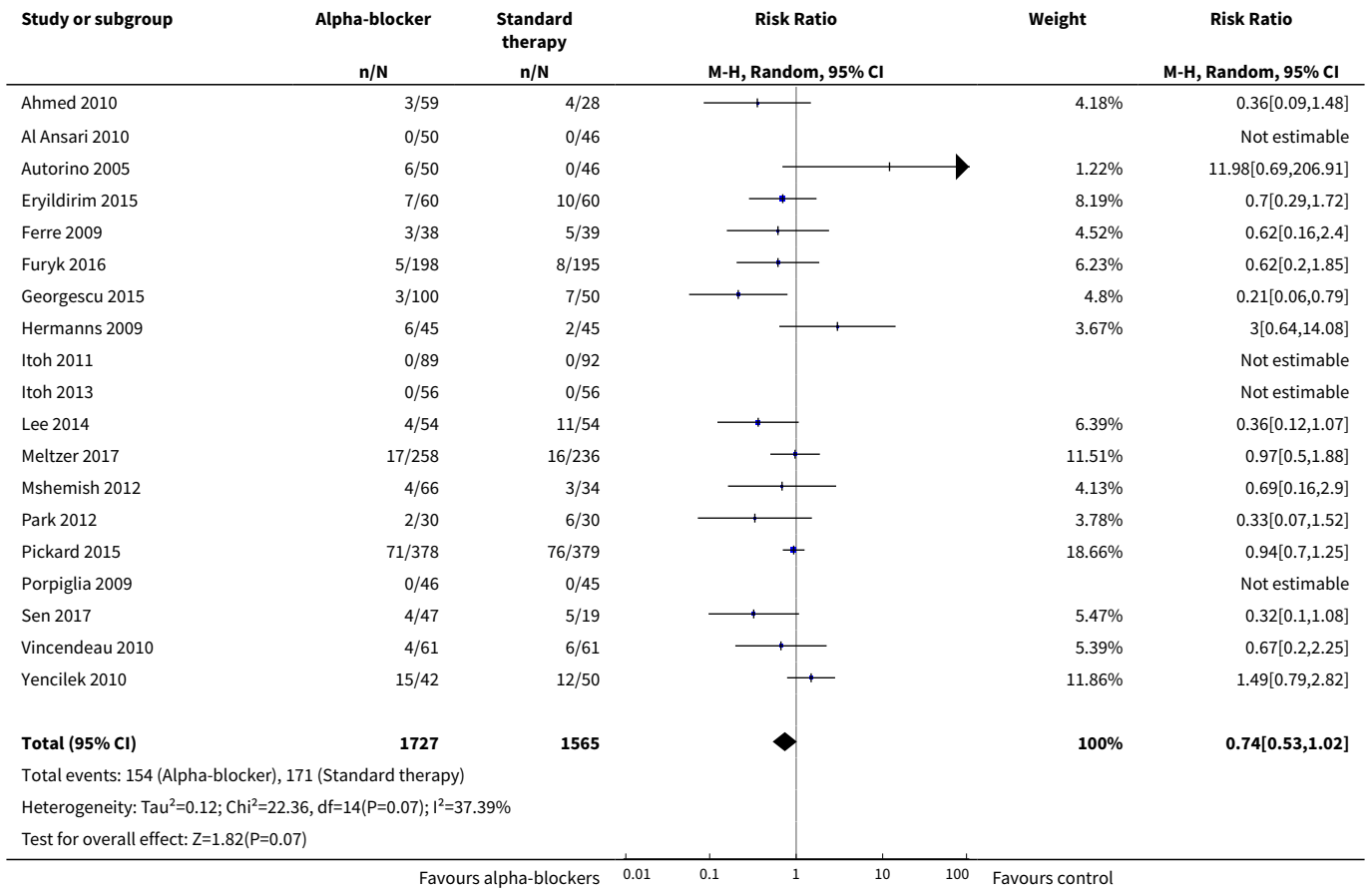
Analysis 1.5. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 5 Dose of diclofenac.



Analysis 1.6. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 6 Hospitalisation.



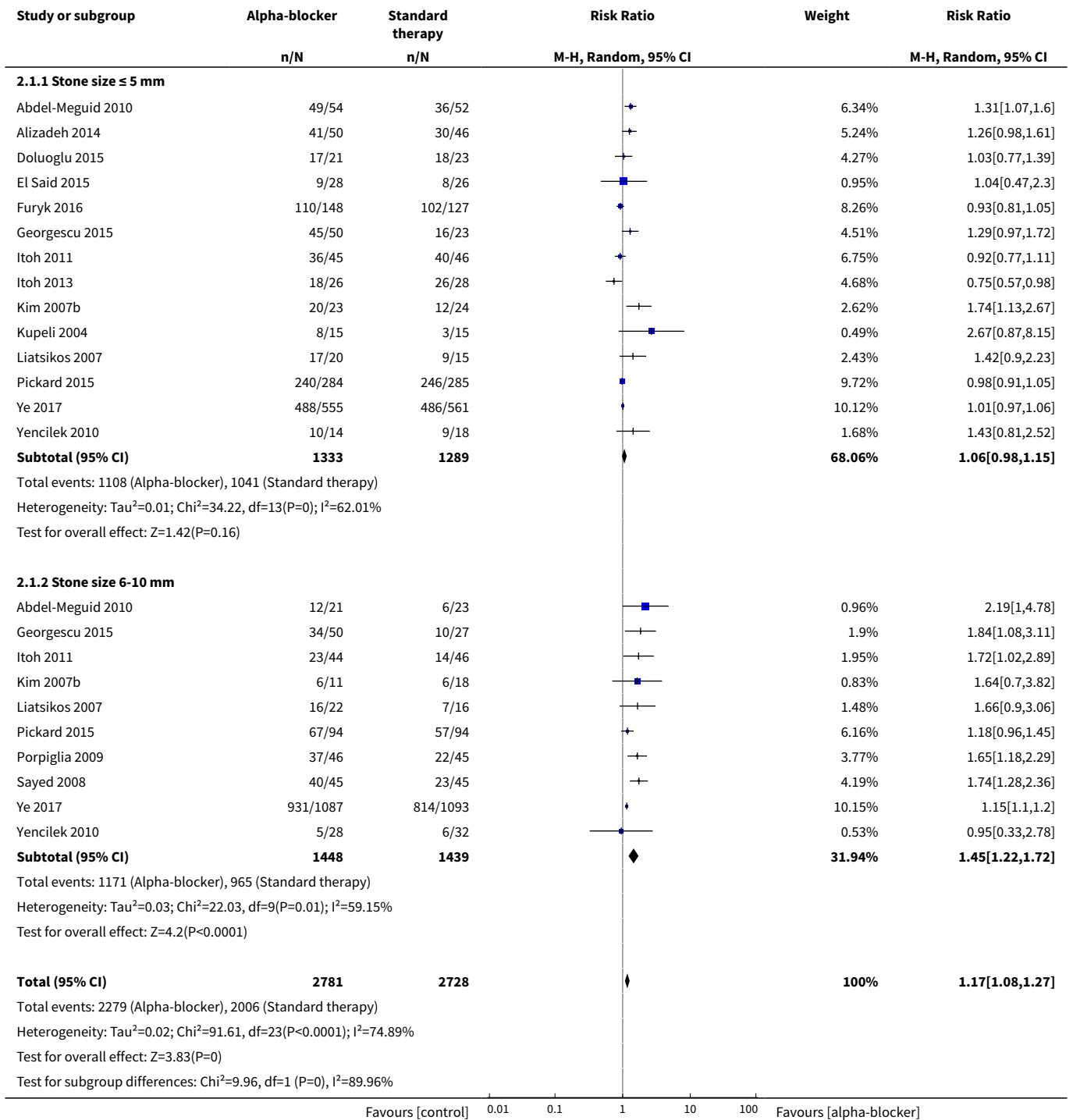
Analysis 1.7. Comparison 1 Alpha-blocker versus standard therapy or placebo, Outcome 7 Surgical intervention.



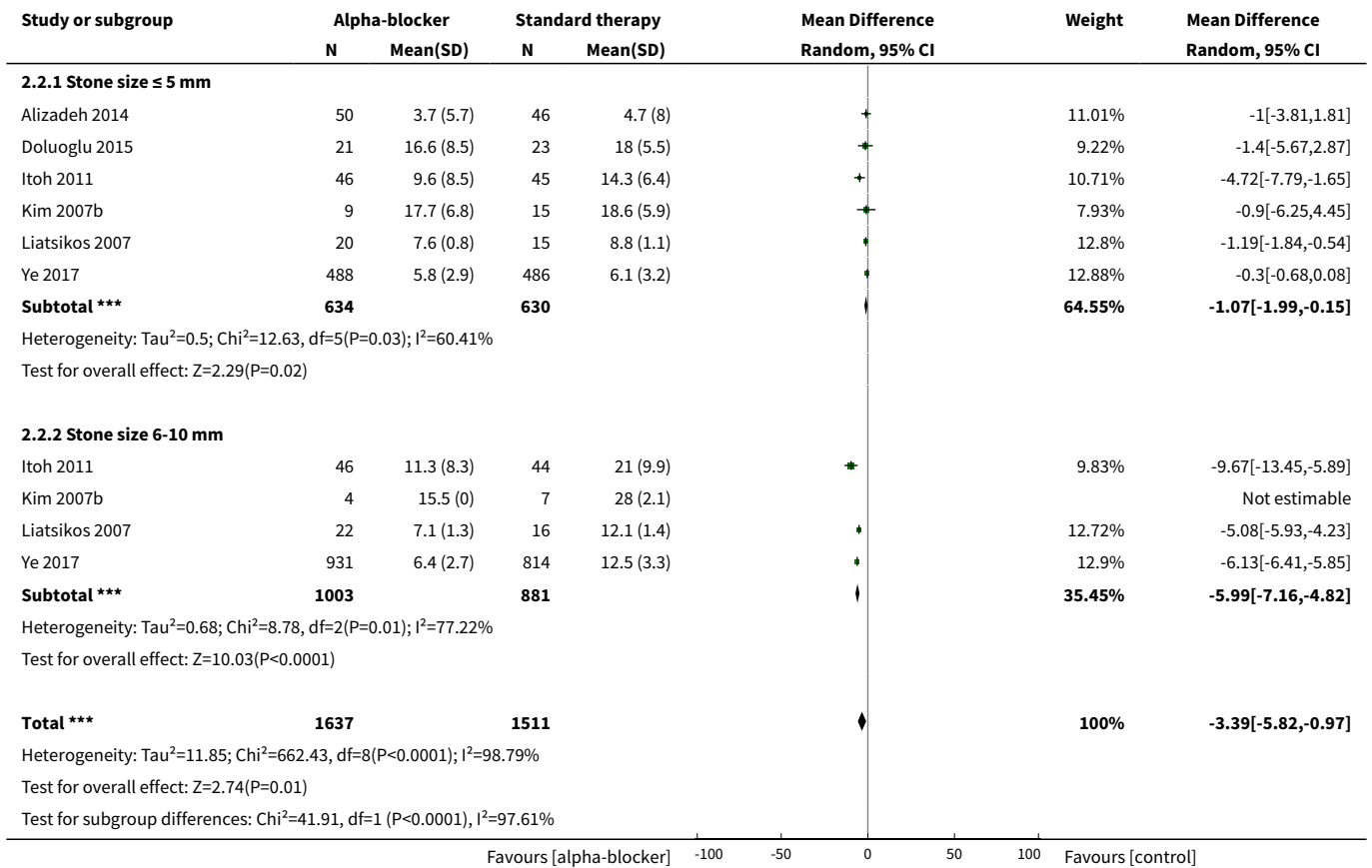
Comparison 2. Subgroup analysis 1: stones measuring 5 mm or less versus stones measuring 6 to 10 mm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	16	5509	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.08, 1.27]
1.1 Stone size ≤ 5 mm	14	2622	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.15]
1.2 Stone size 6-10 mm	10	2887	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.22, 1.72]
2 Stone expulsion time	6	3148	Mean Difference (IV, Random, 95% CI)	-3.39 [-5.82, -0.97]
2.1 Stone size ≤ 5 mm	6	1264	Mean Difference (IV, Random, 95% CI)	-1.07 [-1.99, -0.15]
2.2 Stone size 6-10 mm	4	1884	Mean Difference (IV, Random, 95% CI)	-5.99 [-7.16, -4.82]

Analysis 2.1. Comparison 2 Subgroup analysis 1: stones measuring 5 mm or less versus stones measuring 6 to 10 mm, Outcome 1 Stone clearance.



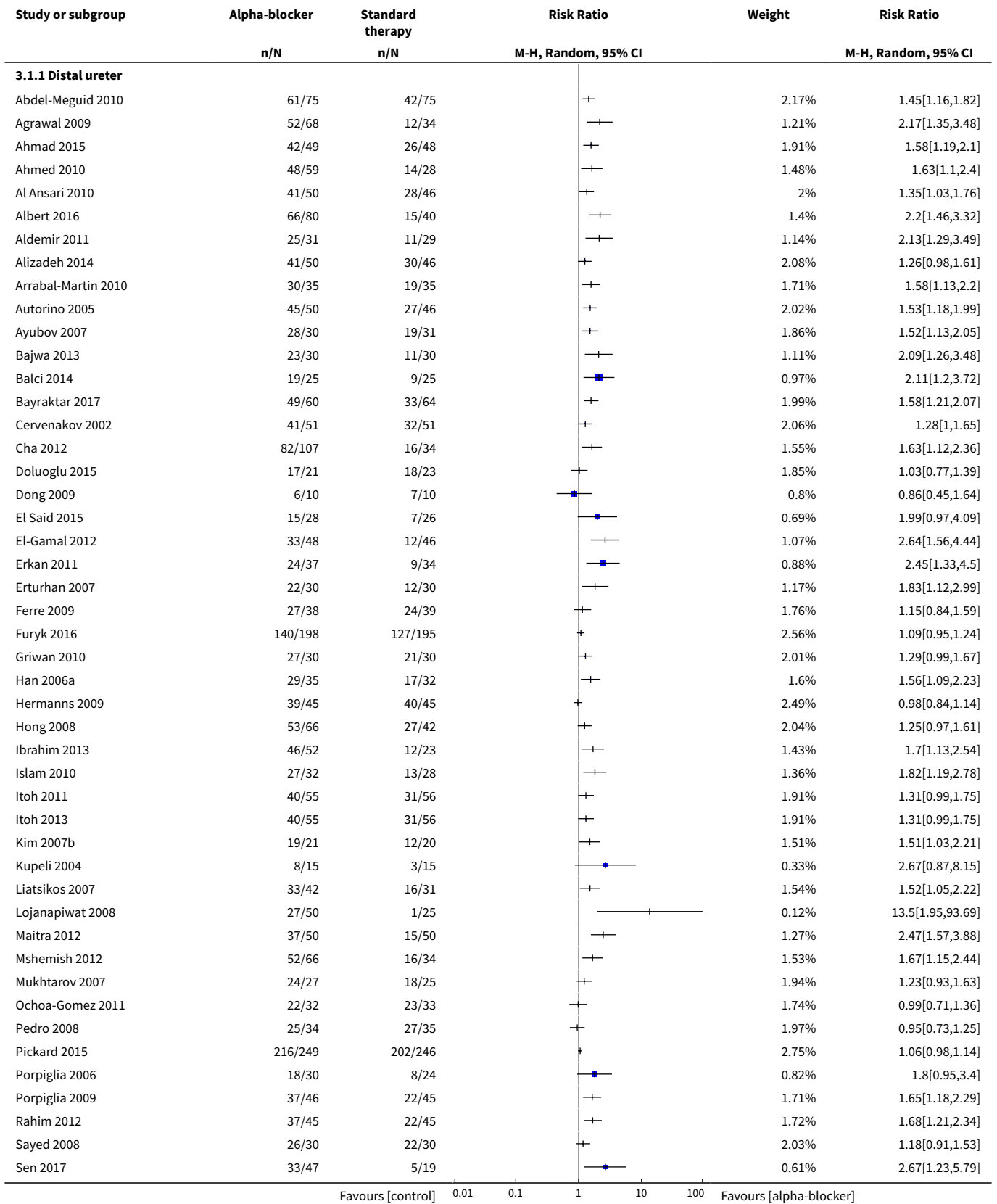
Analysis 2.2. Comparison 2 Subgroup analysis 1: stones measuring 5 mm or less versus stones measuring 6 to 10 mm, Outcome 2 Stone expulsion time.

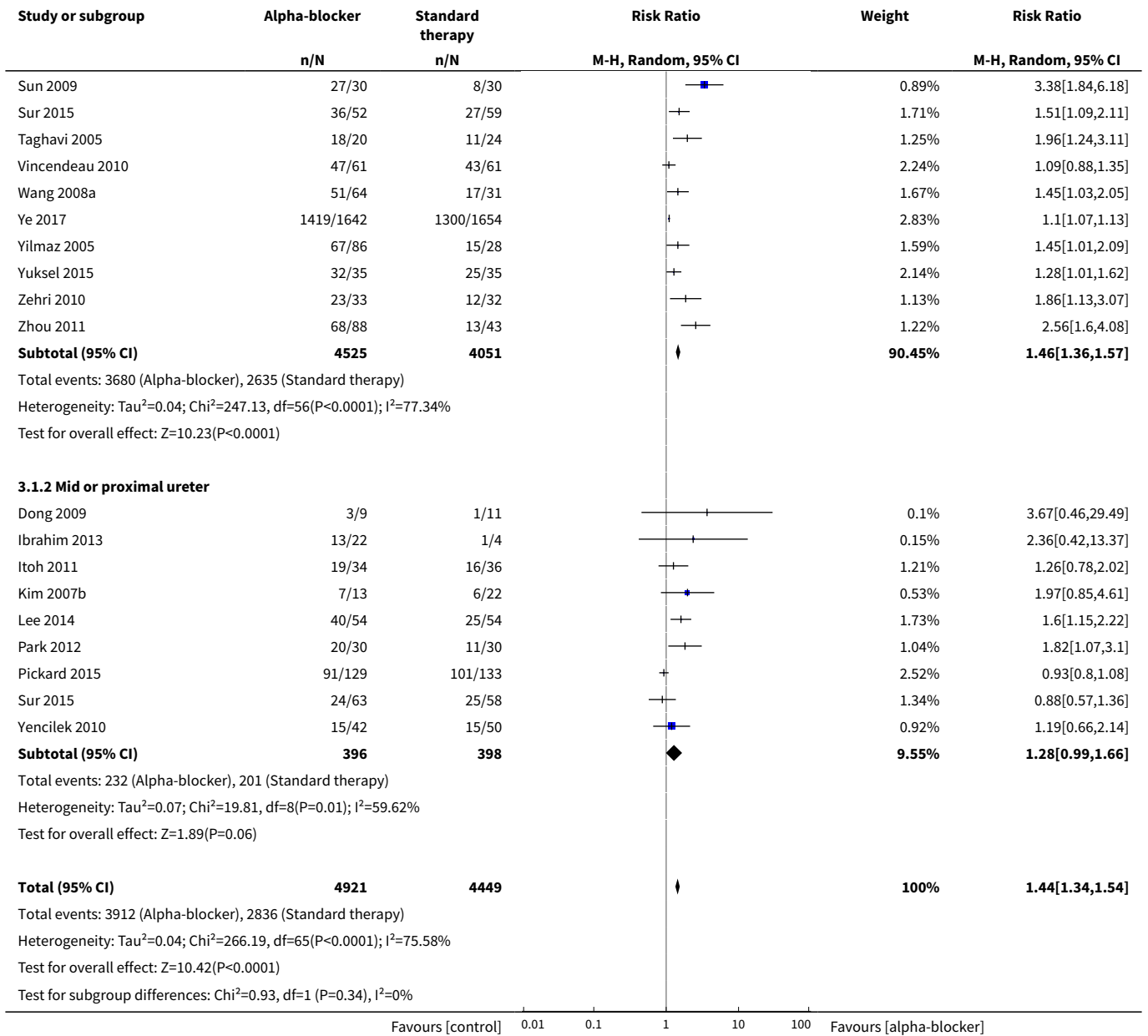


Comparison 3. Subgroup analysis 2: distal ureter versus mid or proximal ureter stones

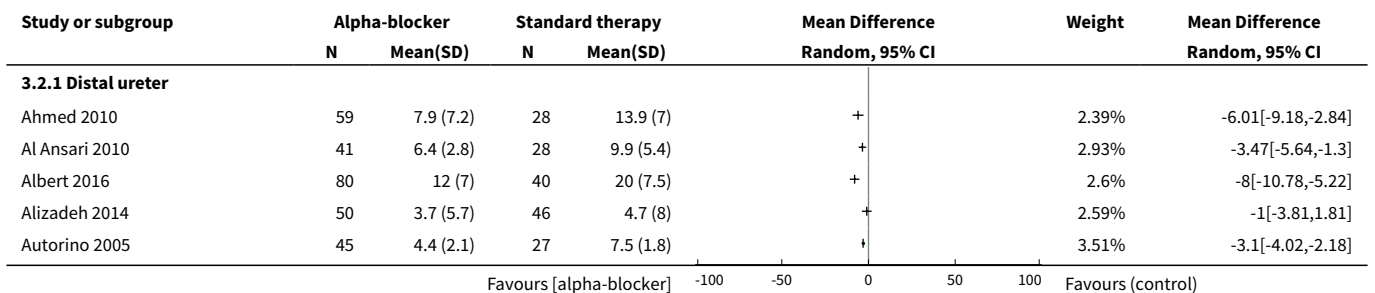
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	60	9370	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.34, 1.54]
1.1 Distal ureter	57	8576	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.36, 1.57]
1.2 Mid or proximal ureter	9	794	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.99, 1.66]
2 Stone expulsion time	32	5599	Mean Difference (IV, Random, 95% CI)	-3.67 [-4.50, -2.85]
2.1 Distal ureter	32	5453	Mean Difference (IV, Random, 95% CI)	-3.43 [-4.26, -2.60]
2.2 Mid or proximal ureter	2	146	Mean Difference (IV, Random, 95% CI)	-8.64 [-19.75, 2.48]

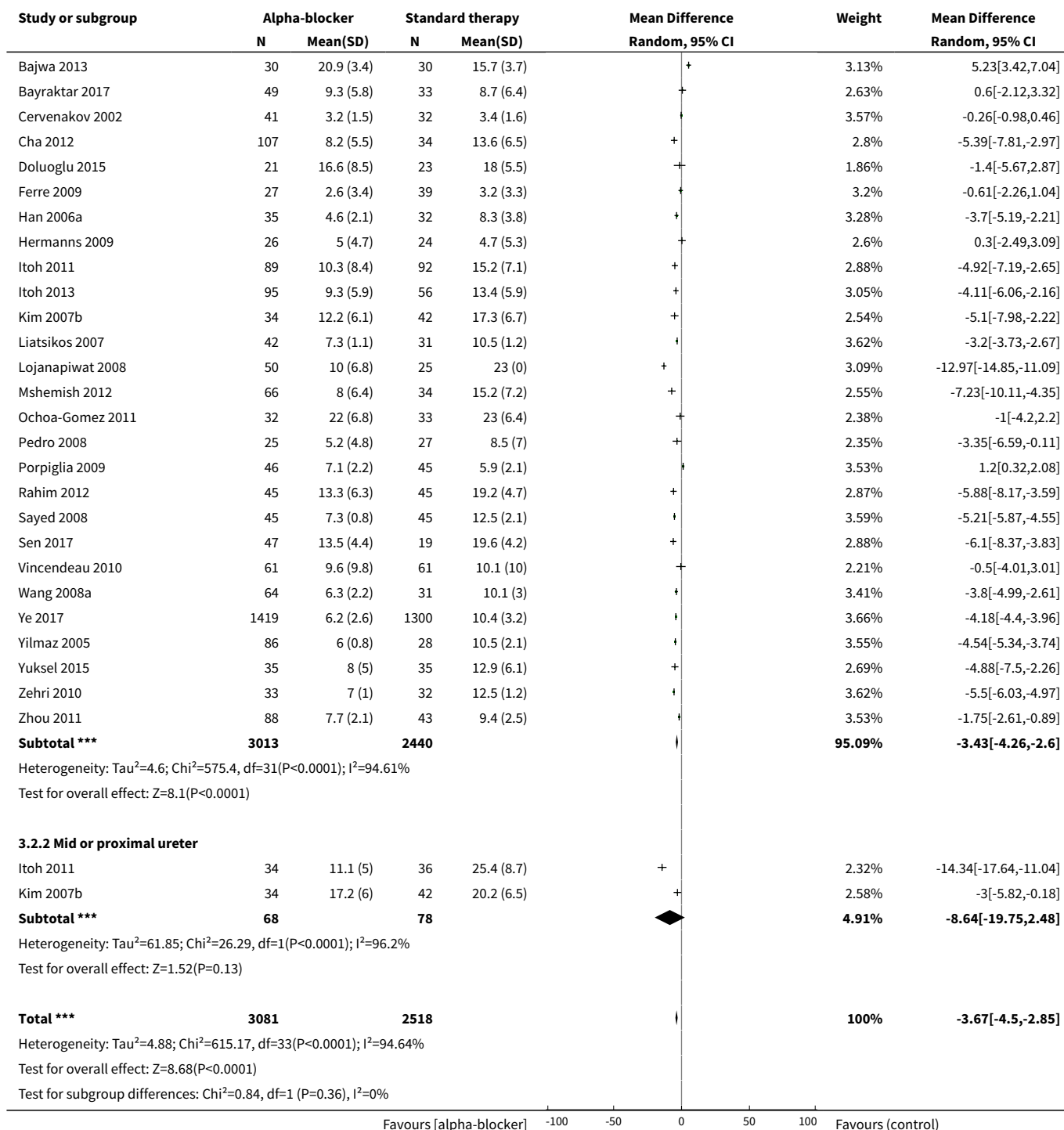
Analysis 3.1. Comparison 3 Subgroup analysis 2: distal ureter versus mid or proximal ureter stones, Outcome 1 Stone clearance.





Analysis 3.2. Comparison 3 Subgroup analysis 2: distal ureter versus mid or proximal ureter stones, Outcome 2 Stone expulsion time.





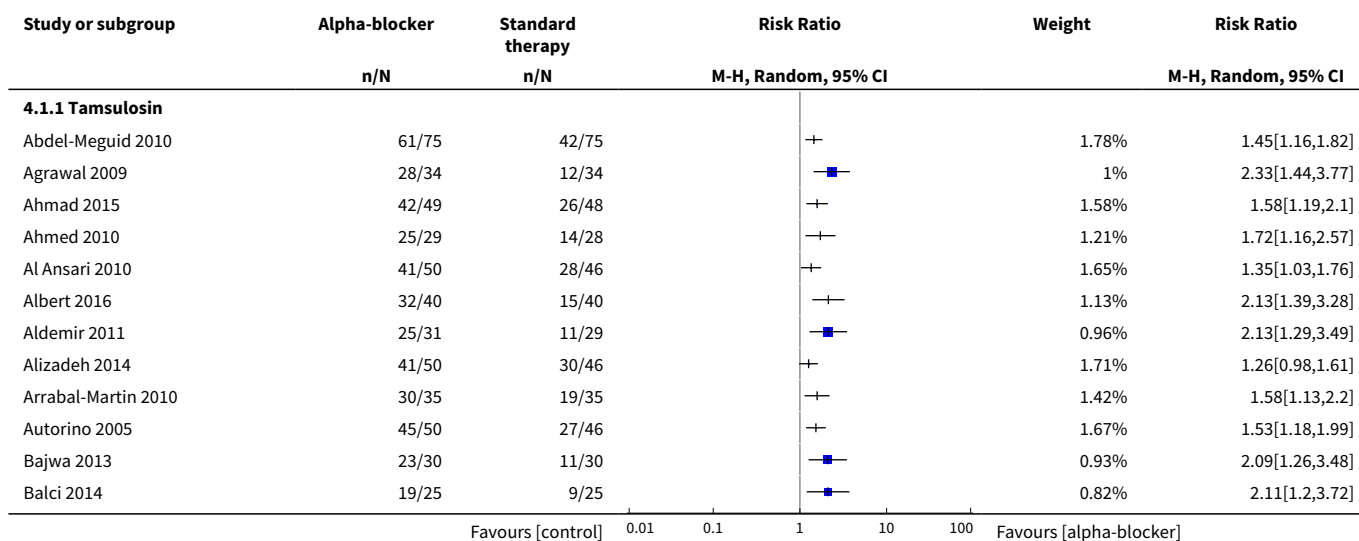
Comparison 4. Subgroup analysis 3: type of alpha-blocker

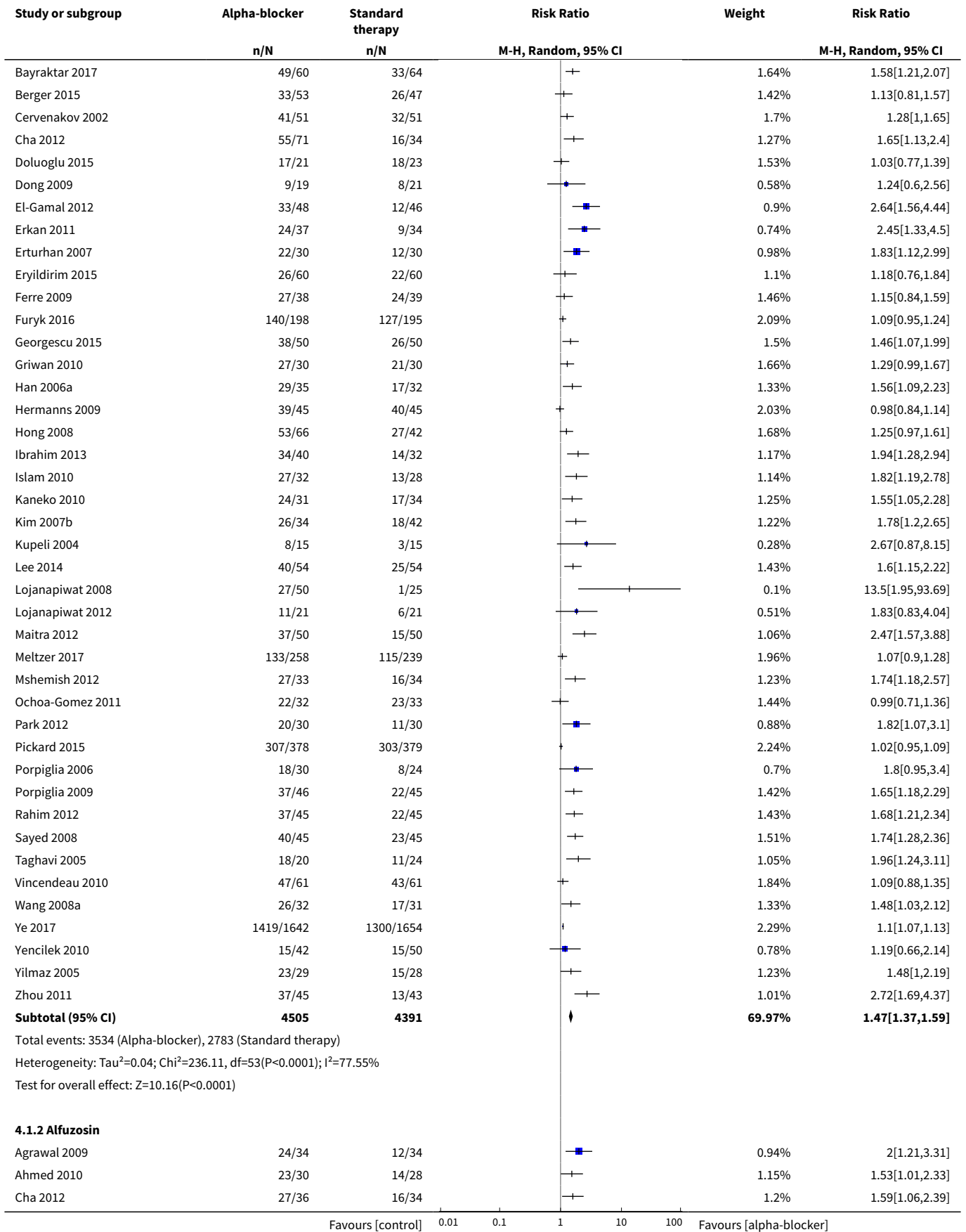
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	67	10897	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.39, 1.58]

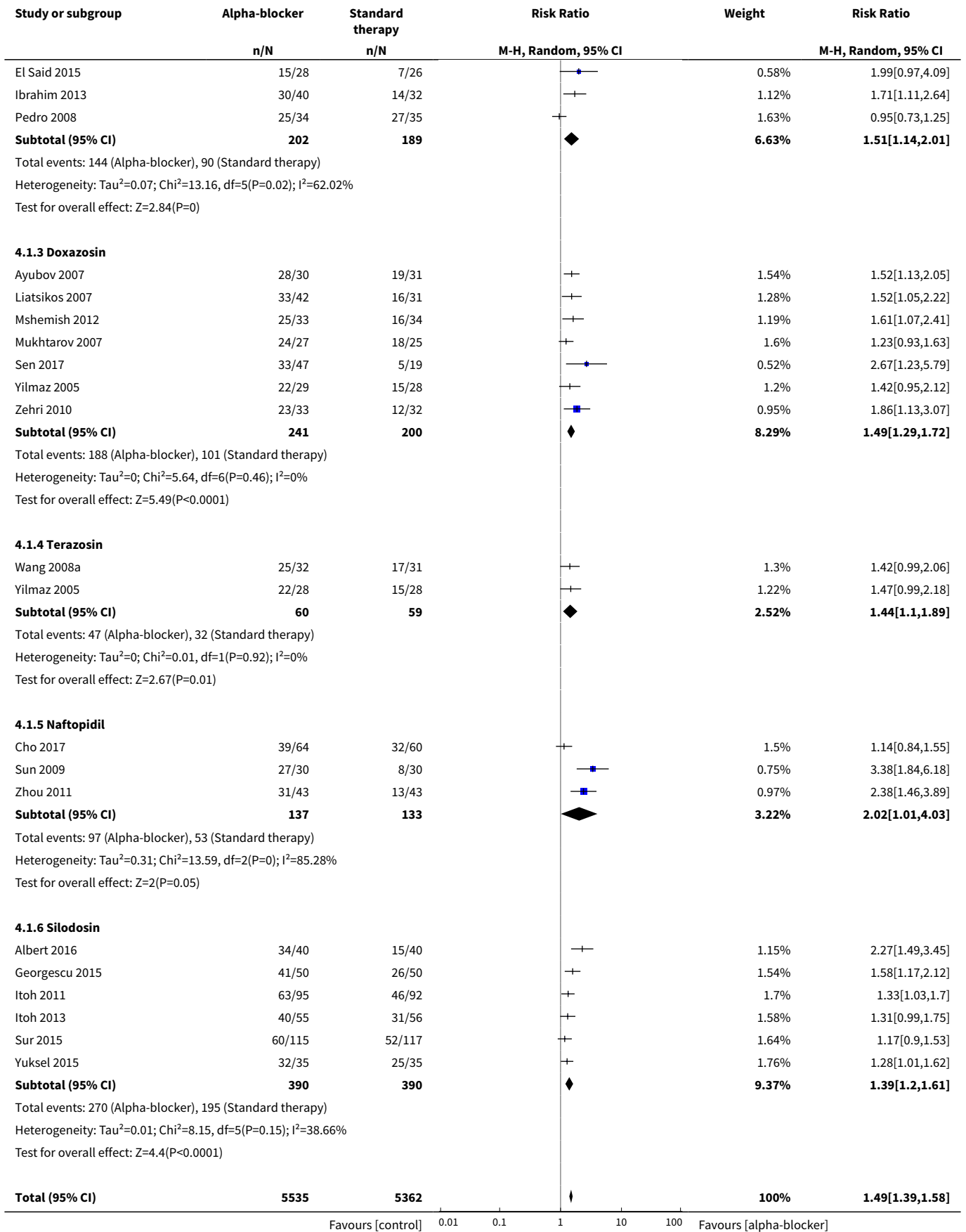
Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Tamsulosin	54	8896	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.37, 1.59]
1.2 Alfuzosin	6	391	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.14, 2.01]
1.3 Doxazosin	7	441	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.29, 1.72]
1.4 Terazosin	2	119	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.10, 1.89]
1.5 Naftopidil	3	270	Risk Ratio (M-H, Random, 95% CI)	2.02 [1.01, 4.03]
1.6 Silodosin	6	780	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.20, 1.61]
2 Major adverse events	18	3003	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.12, 3.48]
2.1 Tamsulosin	13	2062	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.62, 2.47]
2.2 Alfuzosin	5	323	Risk Ratio (M-H, Random, 95% CI)	5.51 [1.46, 20.83]
2.3 Doxazosin	2	133	Risk Ratio (M-H, Random, 95% CI)	3.84 [0.47, 31.11]
2.4 Silodosin	3	361	Risk Ratio (M-H, Random, 95% CI)	6.25 [0.74, 52.57]
2.5 Naftopidil	1	124	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Stone expulsion time	35	6212	Mean Difference (IV, Random, 95% CI)	-3.56 [-4.25, -2.87]
3.1 Tamsulosin	30	5052	Mean Difference (IV, Random, 95% CI)	-3.07 [-4.04, -2.09]
3.2 Alfuzosin	3	180	Mean Difference (IV, Random, 95% CI)	-4.75 [-6.63, -2.88]
3.3 Doxazosin	4	263	Mean Difference (IV, Random, 95% CI)	-4.73 [-6.15, -3.32]
3.4 Terazosin	2	119	Mean Difference (IV, Random, 95% CI)	-4.42 [-5.36, -3.48]
3.5 Naftopidil	1	86	Mean Difference (IV, Random, 95% CI)	-1.80 [-2.80, -0.80]
3.6 Silodosin	4	512	Mean Difference (IV, Random, 95% CI)	-4.98 [-6.43, -3.52]
4 Pain episodes	15	1595	Mean Difference (IV, Random, 95% CI)	-0.71 [-0.89, -0.52]
4.1 Tamsulosin	13	992	Mean Difference (IV, Random, 95% CI)	-0.69 [-0.98, -0.41]
4.2 Alfuzosin	1	58	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.82, 0.18]
4.3 Doxazosin	3	190	Mean Difference (IV, Random, 95% CI)	-0.76 [-0.92, -0.60]
4.4 Terazosin	2	119	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.16, -0.17]
4.5 Naftopidil	1	86	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.23, -0.37]
4.6 Silodosin	2	150	Mean Difference (IV, Random, 95% CI)	-0.89 [-2.05, 0.26]

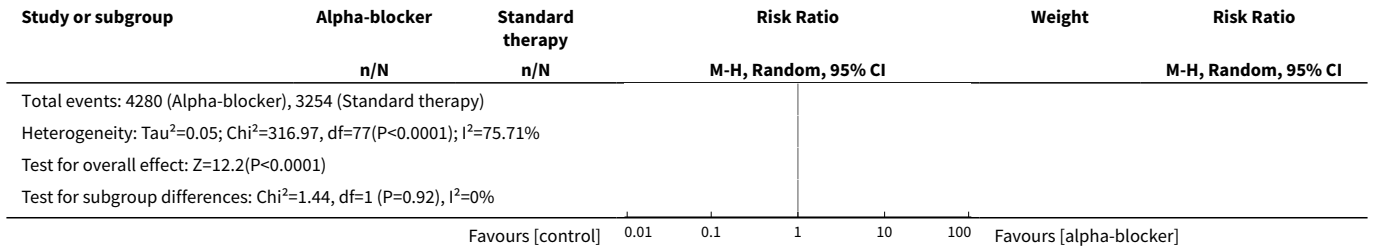
Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
5 Dose of diclofenac [mg]	14	4429	Mean Difference (IV, Random, 95% CI)	-78.11 [-113.25, -42.97]
5.1 Tamsulosin	12	4135	Mean Difference (IV, Random, 95% CI)	-87.60 [-131.98, -43.21]
5.2 Doxazosin	1	57	Mean Difference (IV, Random, 95% CI)	-63.46 [-72.88, -54.04]
5.3 Terazosin	1	56	Mean Difference (IV, Random, 95% CI)	-64.29 [-74.17, -54.41]
5.4 Silodosin	2	181	Mean Difference (IV, Random, 95% CI)	-54.72 [-89.91, -19.53]
6 Hospitalisation	13	2028	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.29, 0.66]
6.1 Tamsulosin	11	1606	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.86]
6.2 Alfuzosin	2	110	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.09, 1.45]
6.3 Doxazosin	2	132	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.05]
6.4 Silodosin	2	180	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.12, 0.55]
7 Surgical intervention	19	3404	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 0.99]
7.1 Tamsulosin	16	2820	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.59, 1.13]
7.2 Alfuzosin	1	58	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.09, 2.35]
7.3 Doxazosin	2	133	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.15, 1.11]
7.4 Silodosin	3	393	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.31]

Analysis 4.1. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 1 Stone clearance.

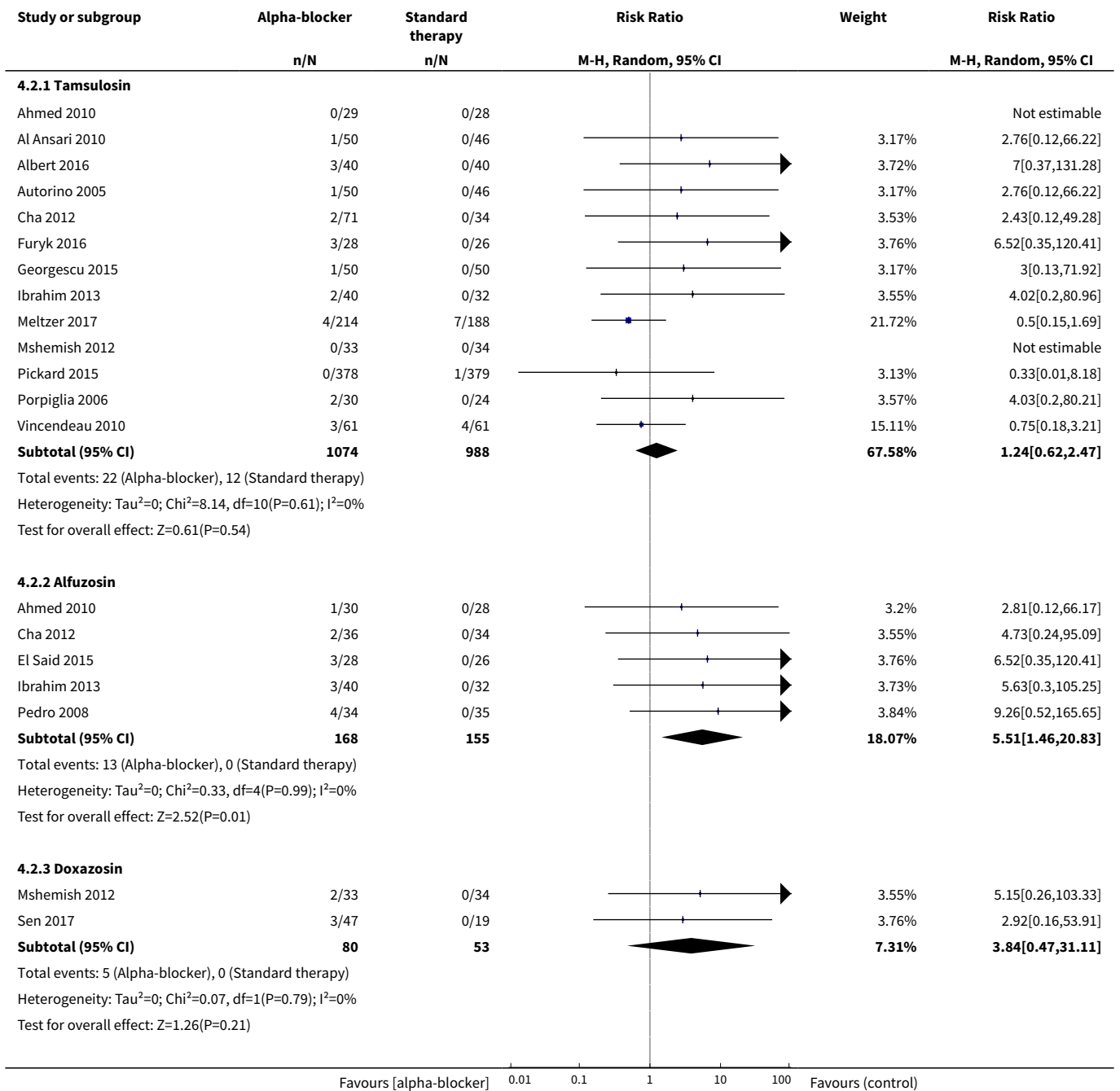


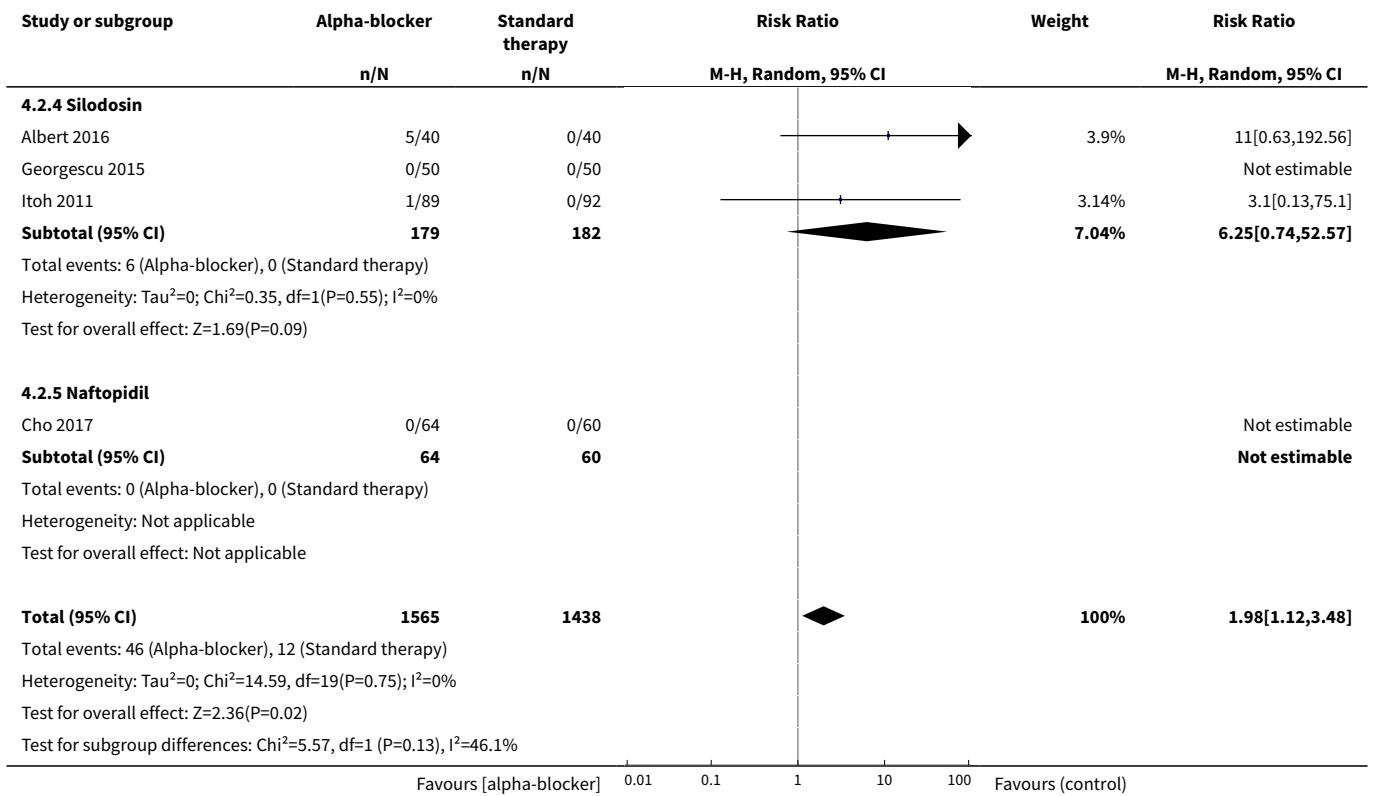






Analysis 4.2. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 2 Major adverse events.





Analysis 4.3. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 3 Stone expulsion time.

Study or subgroup	Alpha-blocker		Standard therapy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)			
4.3.1 Tamsulosin							
Ahmed 2010	29	7.5 (7.1)	28	13.9 (7)	+ 1.63%		-6.38[-10.03,-2.73]
Al Ansari 2010	41	6.4 (2.8)	28	9.9 (5.4)	+ 2.31%		-3.47[-5.64,-1.3]
Albert 2016	40	12 (6.5)	40	20 (7.5)	+ 1.88%		-8[-11.08,-4.92]
Alizadeh 2014	50	3.7 (5.7)	46	4.7 (8)	+ 2%		-1[-3.81,1.81]
Autorino 2005	45	4.4 (2.1)	27	7.5 (1.8)	+ 2.84%		-3.1[-4.02,-2.18]
Bajwa 2013	30	20.9 (3.4)	30	15.7 (3.7)	+ 2.48%		5.23[3.42,7.04]
Bayraktar 2017	49	9.3 (5.8)	33	8.7 (6.4)	+ 2.04%		0.6[-2.12,3.32]
Cervenakov 2002	41	3.2 (1.5)	32	3.4 (1.6)	+ 2.9%		-0.26[-0.98,0.46]
Cha 2012	71	8.2 (5.3)	34	13.6 (6.5)	+ 2.15%		-5.41[-7.92,-2.9]
Doluoglu 2015	21	16.6 (8.5)	23	18 (5.5)	+ 1.4%		-1.4[-5.67,2.87]
Ferre 2009	27	2.6 (3.4)	39	3.2 (3.3)	+ 2.56%		-0.61[-2.26,1.04]
Georgescu 2015	50	9 (5.3)	50	12 (6.2)	+ 2.27%		-3.03[-5.29,-0.77]
Han 2006a	35	4.6 (2.1)	32	8.3 (3.8)	+ 2.63%		-3.7[-5.19,-2.21]
Hermanns 2009	26	5 (4.7)	24	4.7 (5.3)	+ 2.01%		0.3[-2.49,3.09]
Kaneko 2010	31	14 (8.5)	34	17 (11)	+ 1.24%		-3[-7.76,1.76]
Kim 2007b	34	12.7 (6.6)	42	18.5 (6.9)	+ 1.89%		-5.8[-8.85,-2.75]
Lee 2014	54	14.3 (7.9)	54	19.6 (8.5)	+ 1.87%		-5.3[-8.4,-2.2]
Lojanapiwat 2008	50	10 (6.8)	25	23 (0)	+ 2.45%		-12.97[-14.85,-11.09]
Mshemish 2012	33	7.9 (6.4)	34	15.2 (7.2)	+ 1.79%		-7.36[-10.63,-4.09]
Ochoa-Gomez 2011	32	22 (6.8)	33	23 (6.4)	+ 1.83%		-1[-4.2,2.2]

Favours [alpha-blocker] -100 -50 0 50 100 Favours (control)

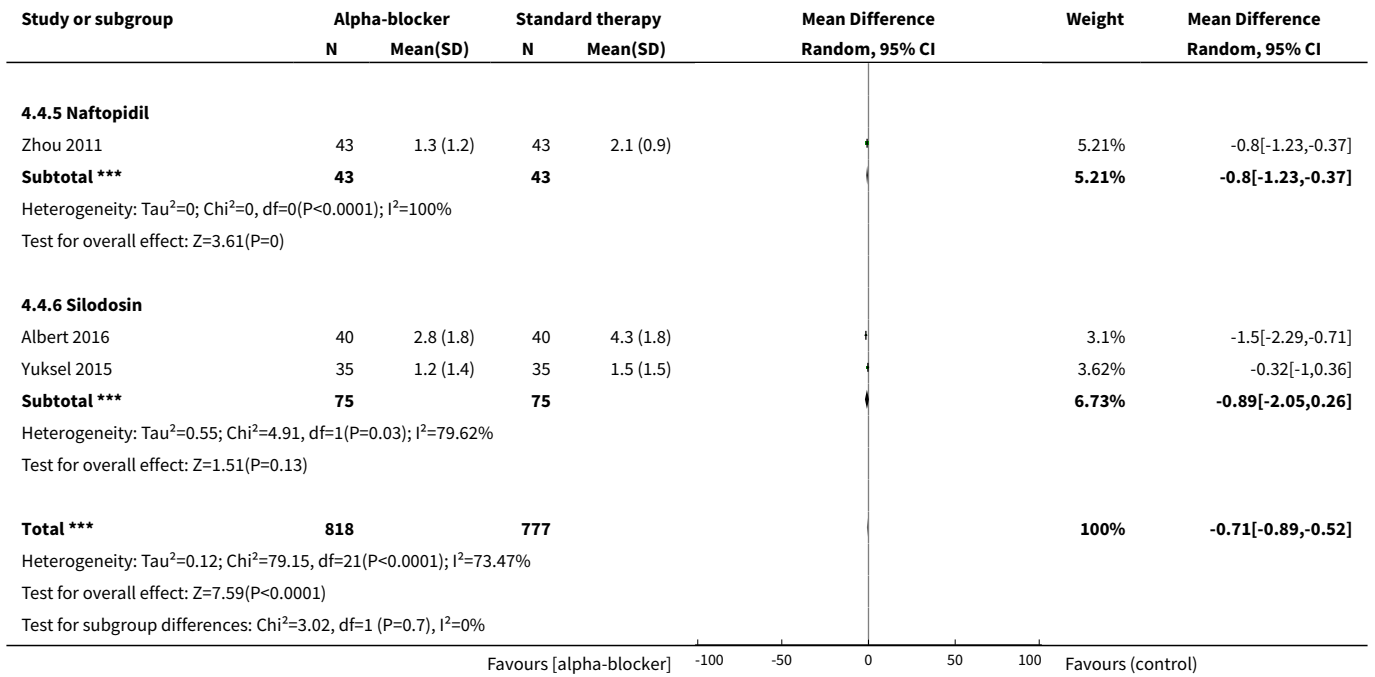
Study or subgroup	Alpha-blocker		Standard therapy		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Pickard 2015	79	16.5 (12.6)	84	15.9 (11.3)	+	1.62%	0.6[-3.08,4.28]
Porpiglia 2009	46	7.1 (2.2)	45	5.9 (2.1)	+	2.85%	1.2[0.32,2.08]
Rahim 2012	45	13.3 (6.3)	45	19.2 (4.7)	+	2.25%	-5.88[-8.17,-3.59]
Sayed 2008	45	7.3 (0.8)	45	12.5 (2.1)	+	2.91%	-5.21[-5.87,-4.55]
Vincendeau 2010	61	9.6 (9.8)	61	10.1 (10)	+	1.69%	-0.5[-4.01,3.01]
Wang 2008a	32	6.3 (2.4)	31	10.1 (3)	+	2.69%	-3.8[-5.14,-2.46]
Ye 2017	1419	6.2 (2.6)	1300	10.4 (3.2)	+	2.98%	-4.18[-4.4,-3.96]
Yencilek 2010	42	8.4 (3.3)	50	11.6 (4.1)	+	2.62%	-3.2[-4.71,-1.69]
Yilmaz 2005	29	6.3 (0.9)	28	10.5 (2.1)	+	2.86%	-4.23[-5.08,-3.38]
Zhou 2011	45	7.7 (1.9)	43	9.4 (2.5)	+	2.84%	-1.7[-2.63,-0.77]
Subtotal ***	2632		2420		↓	67.5%	-3.07[-4.04,-2.09]
Heterogeneity: Tau ² =6; Chi ² =520.87, df=29(P<0.0001); I ² =94.43%							
Test for overall effect: Z=6.16(P<0.0001)							
4.3.2 Alfuzosin							
Ahmed 2010	30	8.3 (7.3)	28	13.9 (7)	+	1.62%	-5.64[-9.33,-1.95]
Cha 2012	36	8.2 (6)	34	13.6 (6.5)	+	1.95%	-5.34[-8.26,-2.42]
Pedro 2008	25	5.2 (4.8)	27	8.5 (7)	+	1.8%	-3.35[-6.59,-0.11]
Subtotal ***	91		89		↓	5.37%	-4.75[-6.63,-2.88]
Heterogeneity: Tau ² =0; Chi ² =1.1, df=2(P=0.58); I ² =0%							
Test for overall effect: Z=4.98(P<0.0001)							
4.3.3 Doxazosin							
Liatsikos 2007	42	7.3 (1.1)	31	10.5 (1.2)	+	2.94%	-3.2[-3.73,-2.67]
Mshemish 2012	33	8.1 (5.7)	34	15.2 (7.2)	+	1.87%	-7.11[-10.21,-4.01]
Sen 2017	47	13.5 (4.4)	19	19.6 (4.2)	+	2.26%	-6.1[-8.37,-3.83]
Yilmaz 2005	29	5.9 (0.6)	28	10.5 (2.1)	+	2.87%	-4.61[-5.42,-3.8]
Subtotal ***	151		112		↓	9.95%	-4.73[-6.15,-3.32]
Heterogeneity: Tau ² =1.42; Chi ² =16.95, df=3(P=0); I ² =82.31%							
Test for overall effect: Z=6.55(P<0.0001)							
4.3.4 Terazosin							
Wang 2008a	32	6.3 (2.1)	31	10.1 (3)	+	2.71%	-3.8[-5.08,-2.52]
Yilmaz 2005	28	5.8 (0.9)	28	10.5 (2.1)	+	2.86%	-4.79[-5.64,-3.94]
Subtotal ***	60		59		↓	5.58%	-4.42[-5.36,-3.48]
Heterogeneity: Tau ² =0.18; Chi ² =1.59, df=1(P=0.21); I ² =37.12%							
Test for overall effect: Z=9.2(P<0.0001)							
4.3.5 Naftopidil							
Zhou 2011	43	7.6 (2.3)	43	9.4 (2.5)	+	2.82%	-1.8[-2.8,-0.8]
Subtotal ***	43		43		↓	2.82%	-1.8[-2.8,-0.8]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.52(P=0)							
4.3.6 Silodosin							
Albert 2016	40	12 (7)	40	20 (7.5)	+	1.83%	-8[-11.18,-4.82]
Georgescu 2015	50	7.8 (5.2)	50	12 (6.2)	+	2.28%	-4.21[-6.45,-1.97]
Itoh 2011	89	10.3 (8.4)	92	15.2 (7.1)	+	2.26%	-4.92[-7.19,-2.65]
Itoh 2013	95	9.3 (5.9)	56	13.4 (5.9)	+	2.42%	-4.11[-6.06,-2.16]
Subtotal ***	274		238		↓	8.79%	-4.98[-6.43,-3.52]
Heterogeneity: Tau ² =0.78; Chi ² =4.64, df=3(P=0.2); I ² =35.37%							
Test for overall effect: Z=6.7(P<0.0001)							

Favours [alpha-blocker] -100 -50 0 50 100 Favours (control)

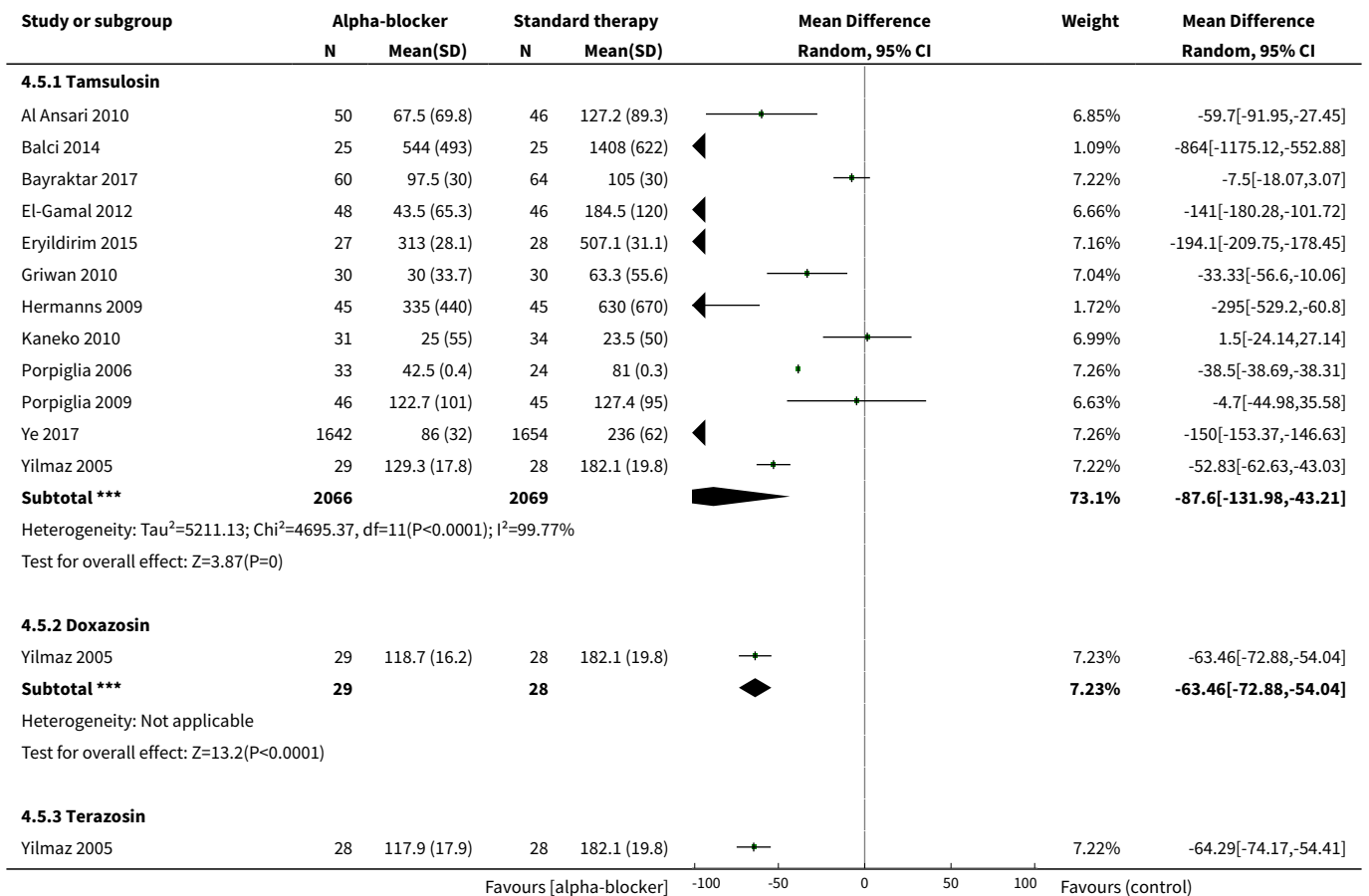
Study or subgroup	Alpha-blocker		Standard therapy		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Total ***	3251		2961			100%	-3.56[-4.25,-2.87]
Heterogeneity: Tau ² =4.16; Chi ² =570.03, df=43(P<0.0001); I ² =92.46%							
Test for overall effect: Z=10.09(P<0.0001)							
Test for subgroup differences: Chi ² =23.76, df=1 (P=0), I ² =78.96%							
Favours [alpha-blocker] -100 -50 0 50 100 Favours (control)							

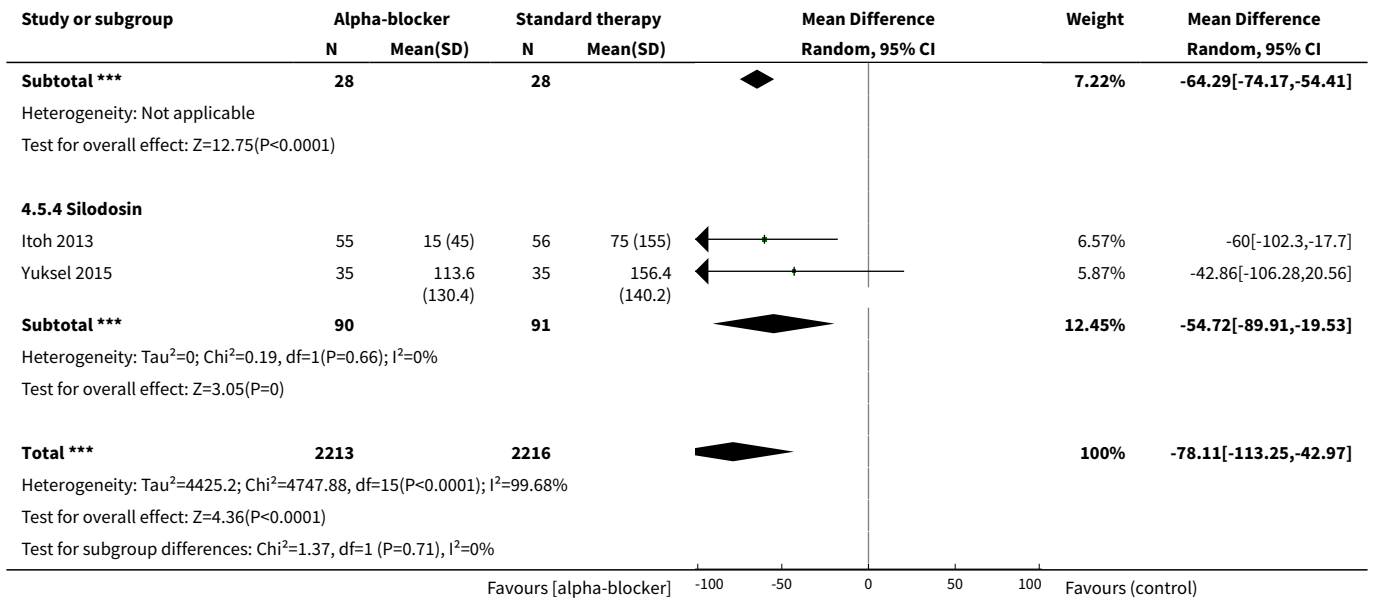
Analysis 4.4. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 4 Pain episodes.

Study or subgroup	Alpha-blocker		Standard therapy		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
4.4.1 Tamsulosin							
Ahmed 2010	29	1.2 (0.6)	28	1.8 (1.2)		4.89%	-0.51[-0.99,-0.03]
Al Ansari 2010	50	1.6 (1.3)	46	2.3 (1.4)		4.48%	-0.7[-1.24,-0.16]
Albert 2016	40	3.1 (1)	40	4.3 (1.8)		3.88%	-1.2[-1.84,-0.56]
Eryildirim 2015	27	3.6 (0.3)	28	4.9 (0.4)		6.89%	-1.33[-1.52,-1.14]
Ferre 2009	35	7.9 (10.1)	34	7.9 (10)		0.14%	0.06[-4.68,4.8]
Griwan 2010	30	0.6 (0.7)	30	1.3 (1.1)		5.01%	-0.67[-1.13,-0.21]
Mshemish 2012	33	1.1 (0.3)	34	2.2 (0.5)		6.77%	-1.02[-1.23,-0.81]
Porpiglia 2009	46	1.4 (1.1)	45	1.1 (1)		5.15%	0.27[-0.17,0.71]
Sayed 2008	45	1.5 (0.3)	45	2.5 (1.4)		5.33%	-0.94[-1.36,-0.52]
Vincendeau 2010	60	2.6 (2.1)	59	2.6 (1.9)		3.44%	0[-0.72,0.72]
Wang 2008a	32	2 (1.5)	31	2.2 (1.6)		3.22%	-0.19[-0.95,0.57]
Yilmaz 2005	29	1.7 (0.9)	28	2.4 (1.4)		4.07%	-0.7[-1.31,-0.09]
Zhou 2011	45	1.2 (1.7)	43	2.1 (0.9)		4.46%	-0.9[-1.44,-0.36]
Subtotal ***	501		491			57.73%	-0.69[-0.98,-0.41]
Heterogeneity: Tau ² =0.19; Chi ² =63, df=12(P<0.0001); I ² =80.95%							
Test for overall effect: Z=4.75(P<0.0001)							
4.4.2 Alfuzosin							
Ahmed 2010	30	1.4 (0.7)	28	1.8 (1.2)		4.79%	-0.32[-0.82,0.18]
Subtotal ***	30		28			4.79%	-0.32[-0.82,0.18]
Heterogeneity: Tau ² =0; Chi ² =0, df=0(P<0.0001); I ² =100%							
Test for overall effect: Z=1.27(P=0.21)							
4.4.3 Doxazosin							
Mshemish 2012	33	1.3 (0.4)	34	2.2 (0.5)		6.64%	-0.84[-1.07,-0.61]
Sen 2017	47	0.6 (0.4)	19	1.3 (0.5)		6.5%	-0.66[-0.91,-0.41]
Yilmaz 2005	29	1.7 (0.2)	28	2.4 (1.4)		4.63%	-0.75[-1.27,-0.23]
Subtotal ***	109		81			17.77%	-0.76[-0.92,-0.6]
Heterogeneity: Tau ² =0; Chi ² =1.08, df=2(P=0.58); I ² =0%							
Test for overall effect: Z=9.25(P<0.0001)							
4.4.4 Terazosin							
Wang 2008a	32	1.8 (1.5)	31	2.2 (1.6)		3.16%	-0.32[-1.1,0.46]
Yilmaz 2005	28	1.6 (0.2)	28	2.4 (1.4)		4.61%	-0.85[-1.37,-0.33]
Subtotal ***	60		59			7.77%	-0.67[-1.16,-0.17]
Heterogeneity: Tau ² =0.03; Chi ² =1.23, df=1(P=0.27); I ² =18.88%							
Test for overall effect: Z=2.64(P=0.01)							
Favours [alpha-blocker] -100 -50 0 50 100 Favours (control)							

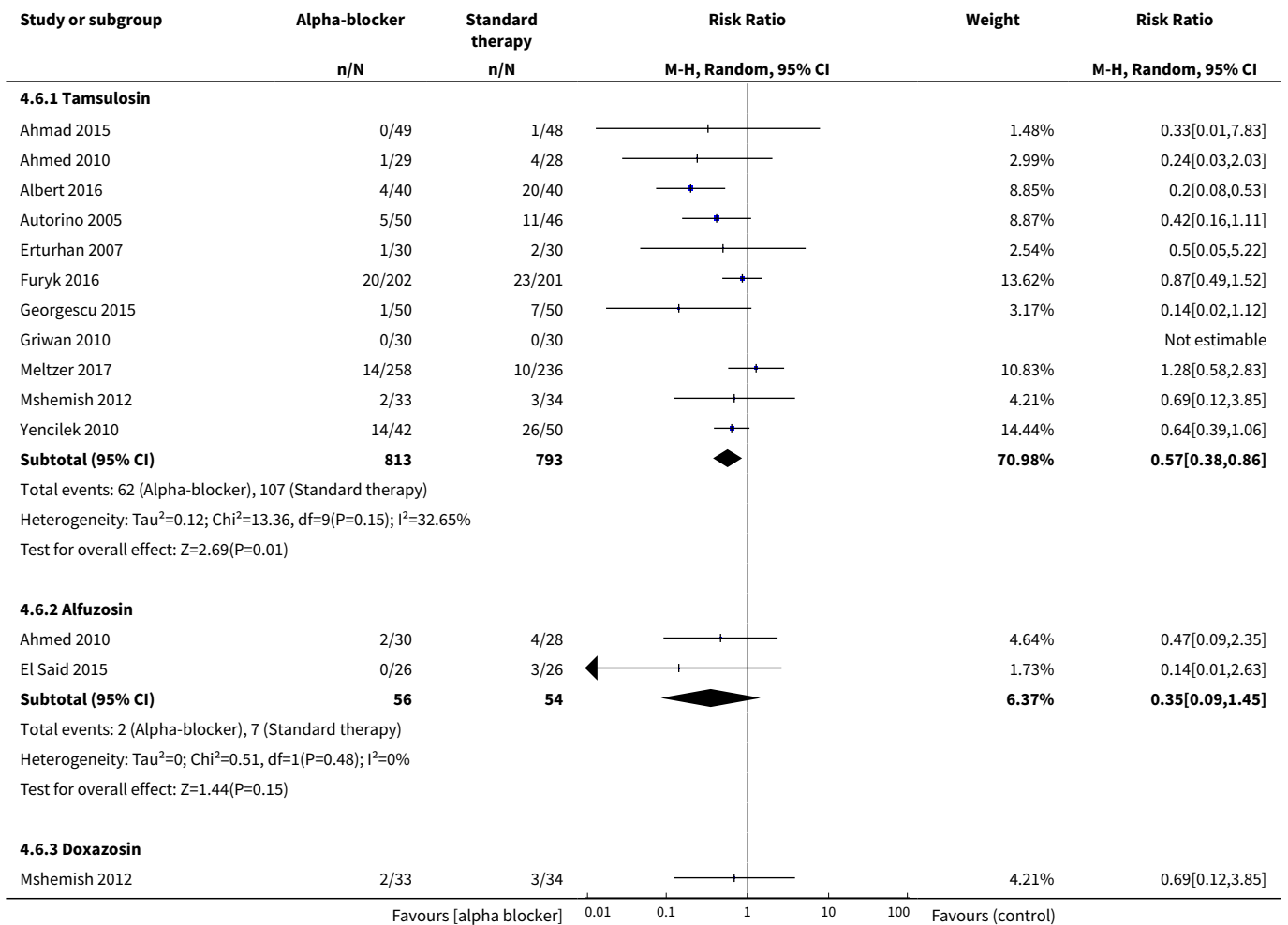


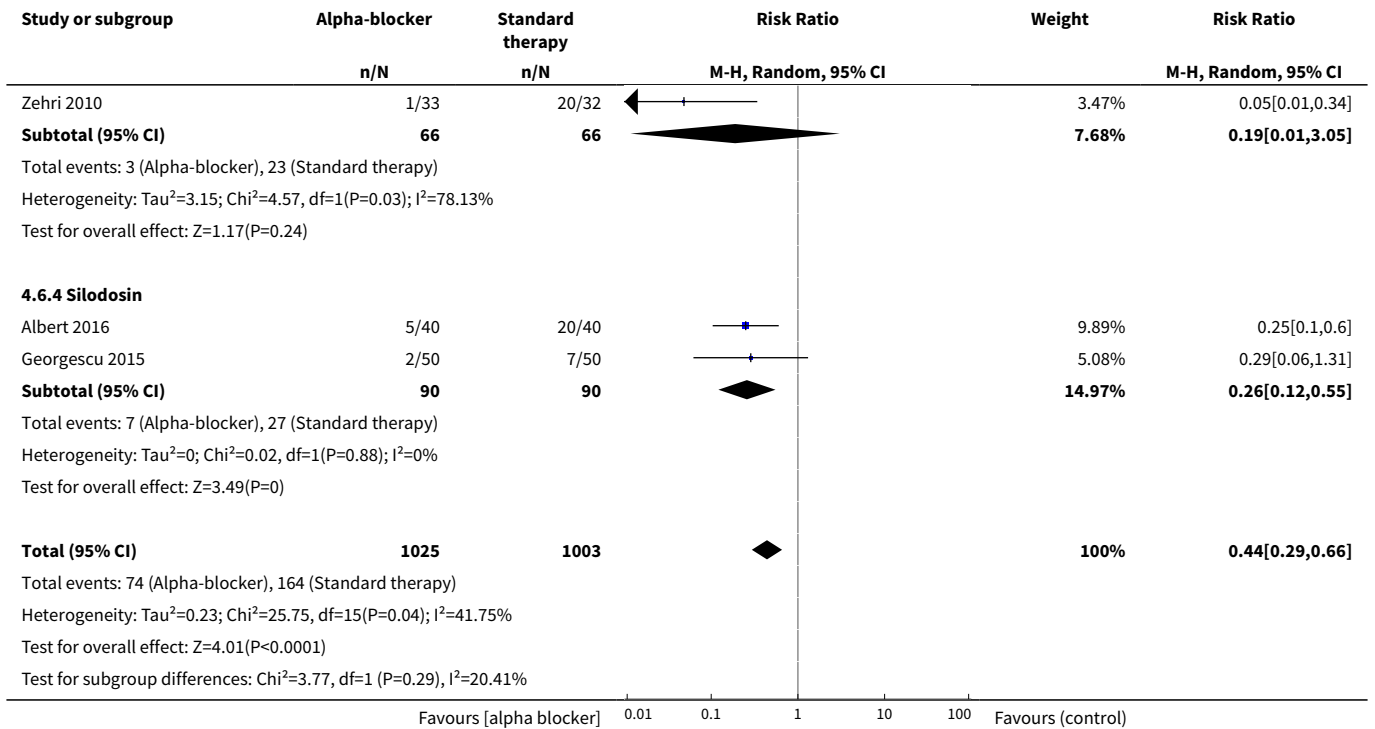
Analysis 4.5. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 5 Dose of diclofenac [mg].



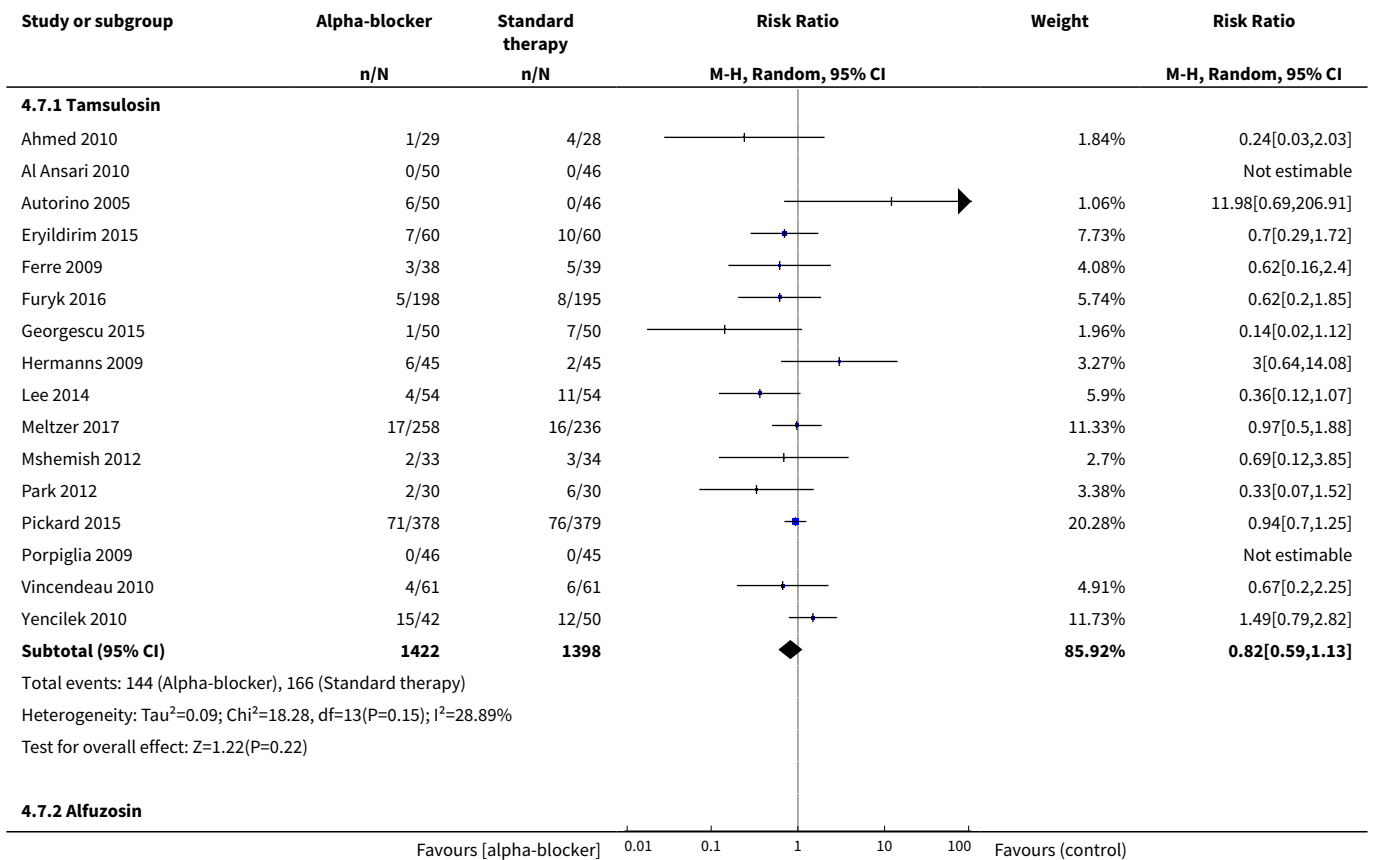


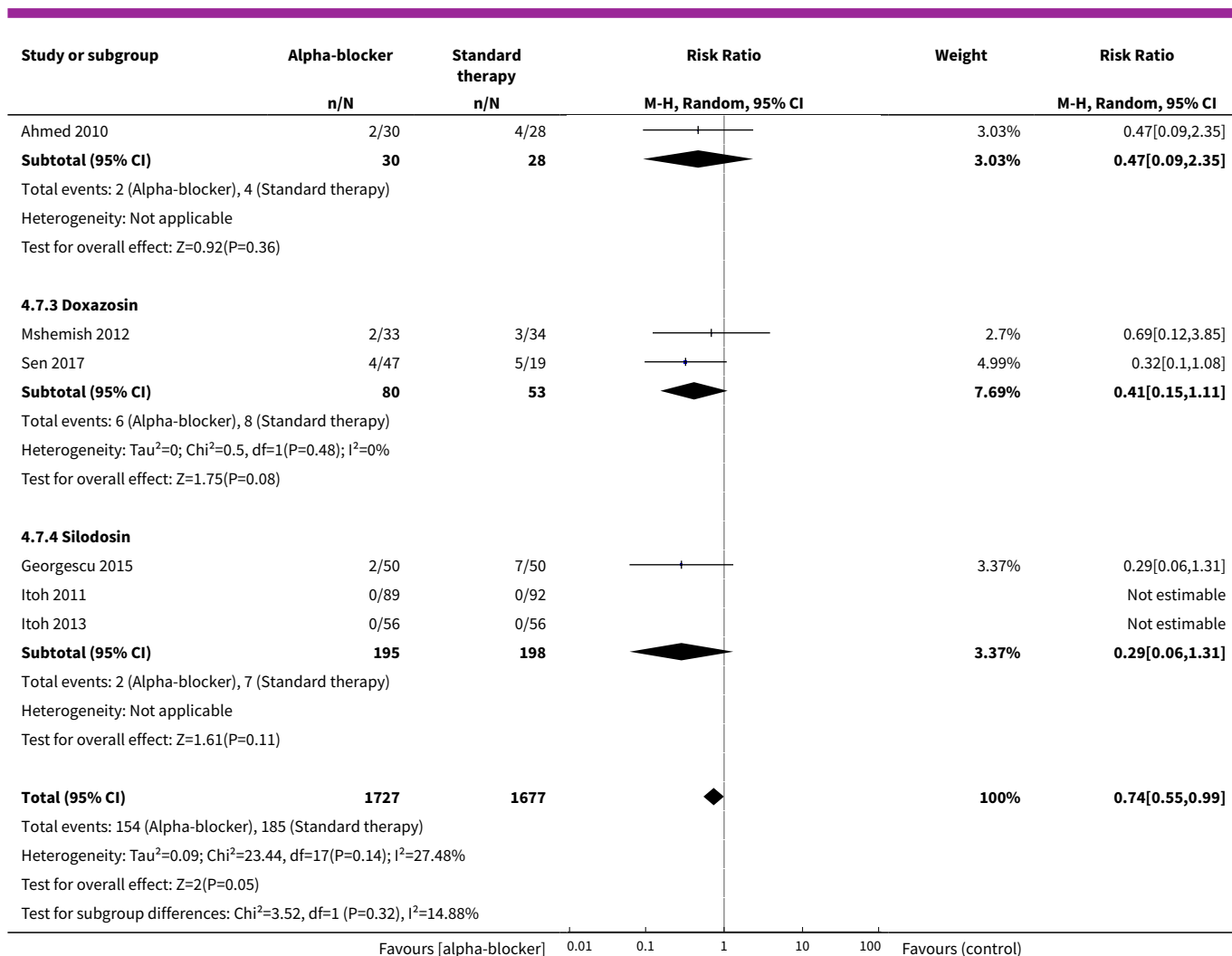
Analysis 4.6. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 6 Hospitalisation.





Analysis 4.7. Comparison 4 Subgroup analysis 3: type of alpha-blocker, Outcome 7 Surgical intervention.

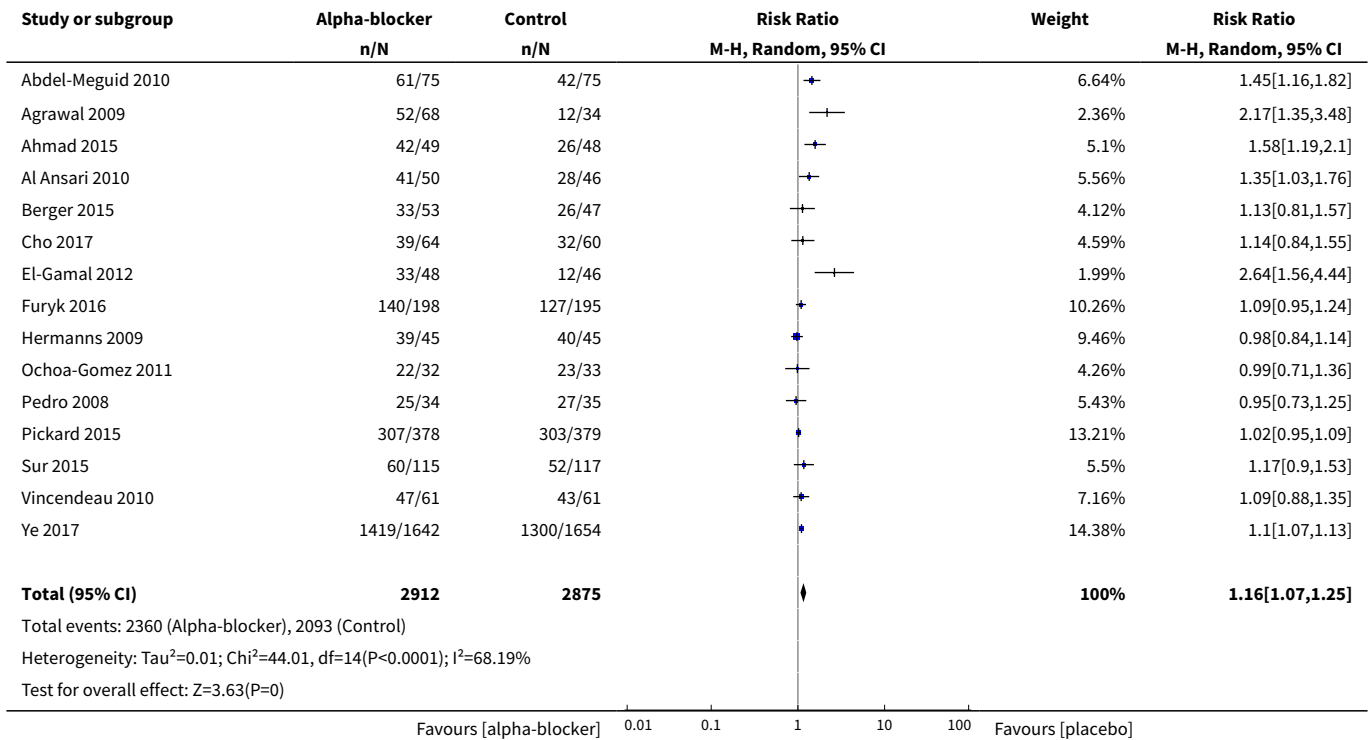




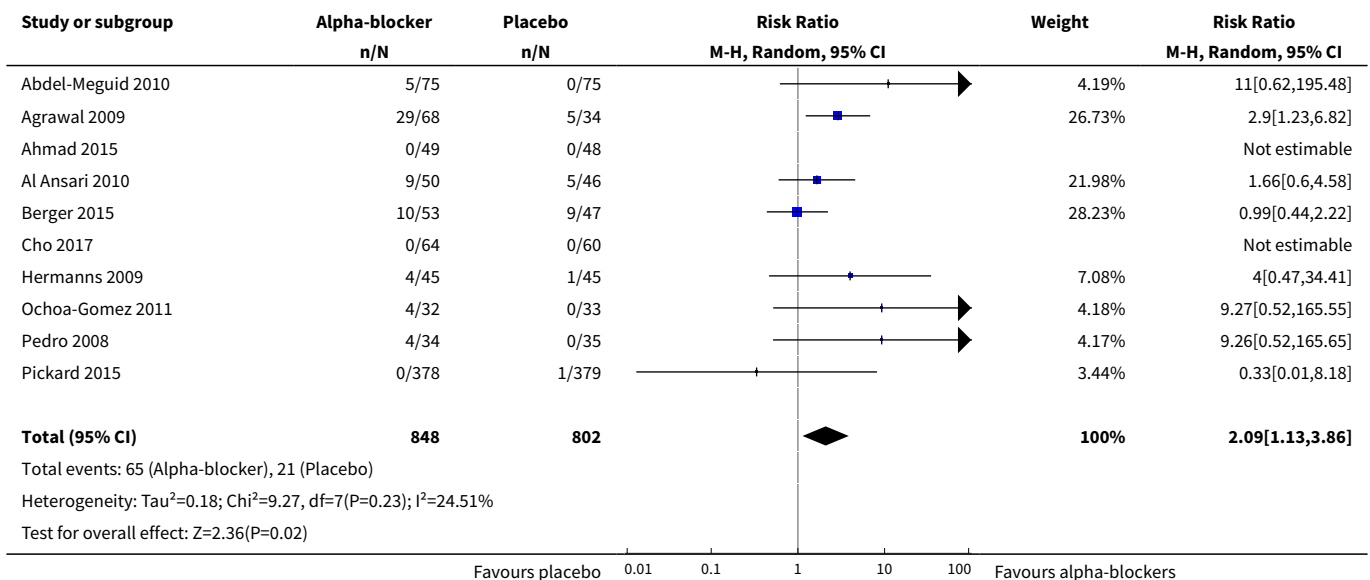
Comparison 5. Sensitivity analysis 1: alpha-blocker versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	15	5787	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.07, 1.25]
2 Major adverse events	10	1650	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.13, 3.86]
3 Stone expulsion time	7	3240	Mean Difference (IV, Random, 95% CI)	-1.98 [-3.71, -0.24]
4 Pain episodes	2	215	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.07, 0.29]
5 Dose of diclofenac	4	3576	Mean Difference (IV, Random, 95% CI)	-126.32 [-181.73, -70.90]
6 Hospitalisation	2	500	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.48, 1.47]
7 Surgical intervention	5	1458	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.70, 1.24]

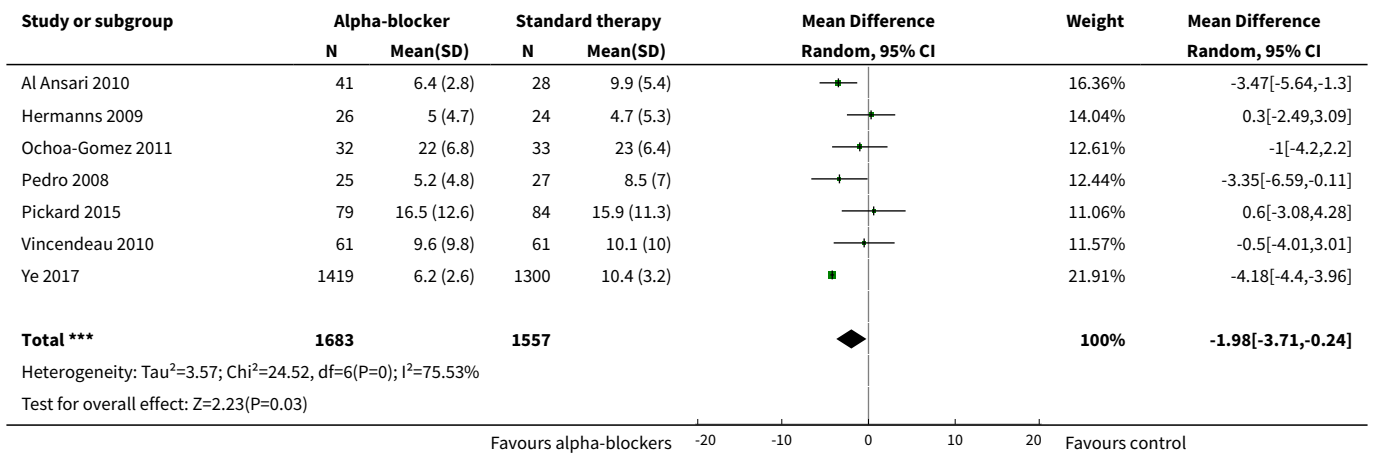
Analysis 5.1. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 1 Stone clearance.



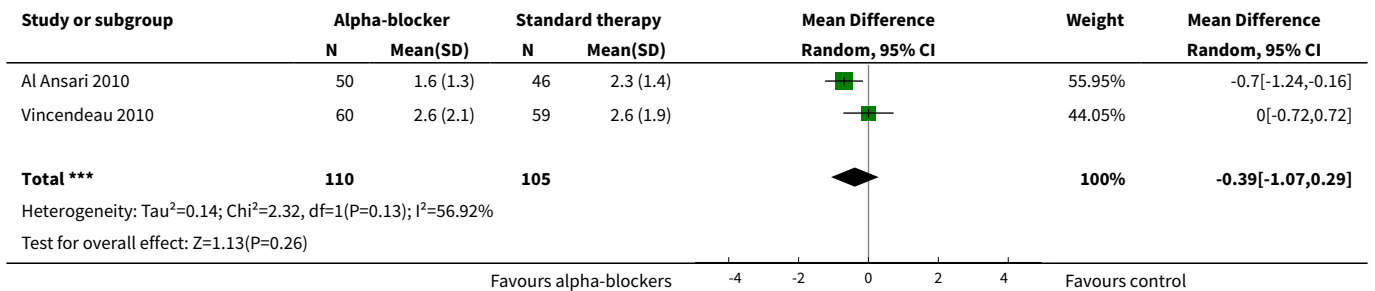
Analysis 5.2. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 2 Major adverse events.



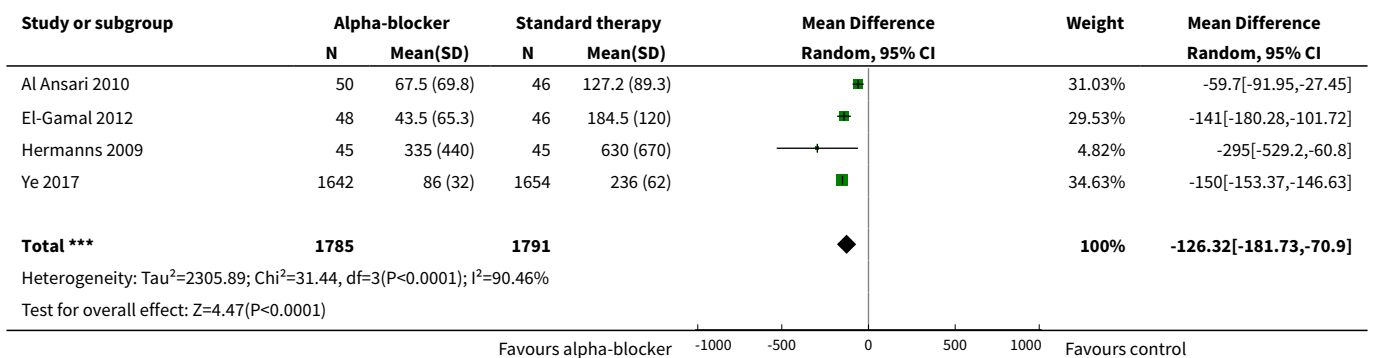
Analysis 5.3. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 3 Stone expulsion time.



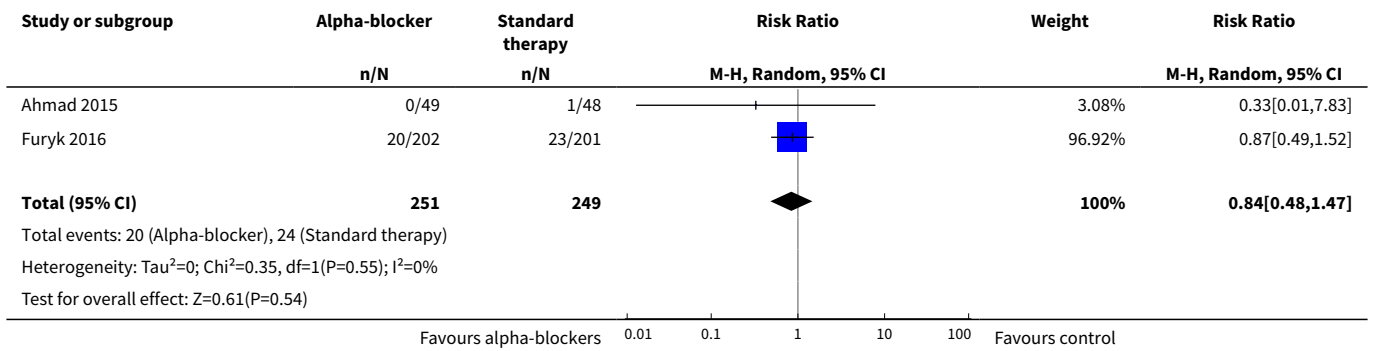
Analysis 5.4. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 4 Pain episodes.



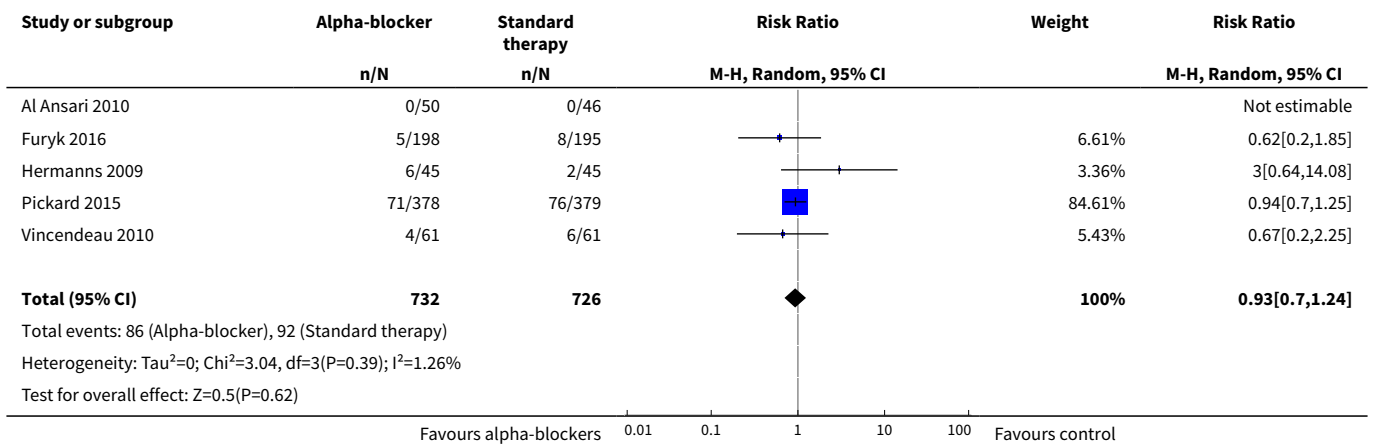
Analysis 5.5. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 5 Dose of diclofenac.



Analysis 5.6. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 6 Hospitalisation.



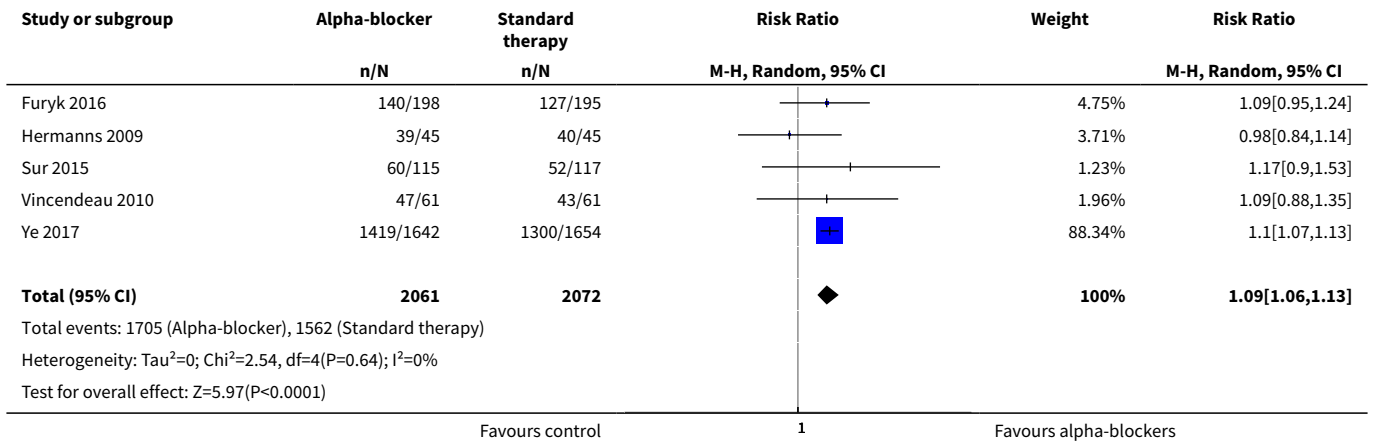
Analysis 5.7. Comparison 5 Sensitivity analysis 1: alpha-blocker versus placebo, Outcome 7 Surgical intervention.



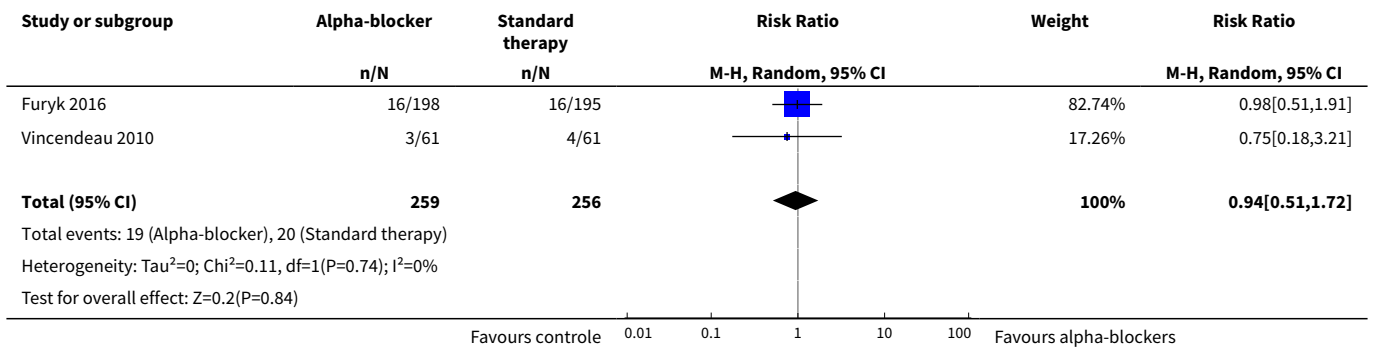
Comparison 6. Sensitivity analysis 2: high-quality studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone clearance	5	4133	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.06, 1.13]
2 Major adverse events	2	515	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.51, 1.72]
3 Stone expulsion time	3	2891	Mean Difference (IV, Random, 95% CI)	-1.72 [-5.13, 1.68]
4 Pain episodes	1	119	Mean Difference (IV, Random, 95% CI)	0.0 [-0.72, 0.72]
5 Dose of diclofenac	2	3386	Mean Difference (IV, Random, 95% CI)	-173.28 [-277.60, -68.95]
6 Hospitalisation	1	403	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.49, 1.52]
7 Surgical intervention	3	605	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.32]

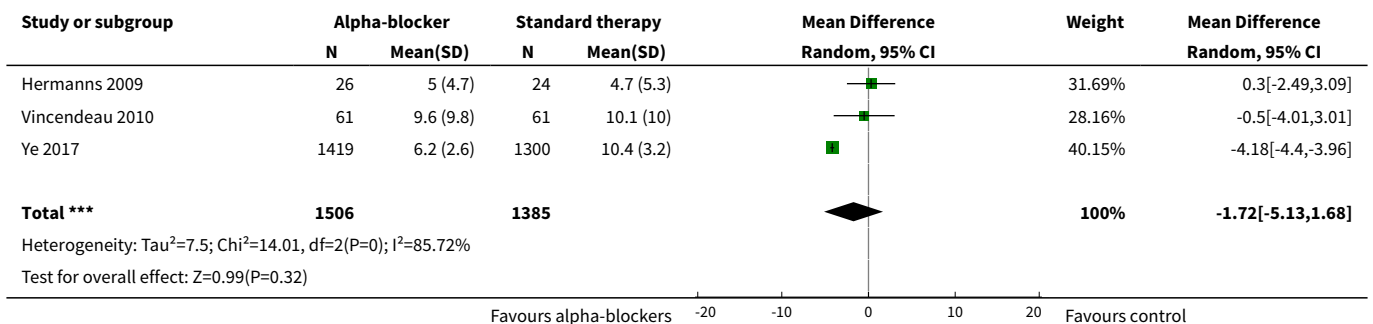
Analysis 6.1. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 1 Stone clearance.



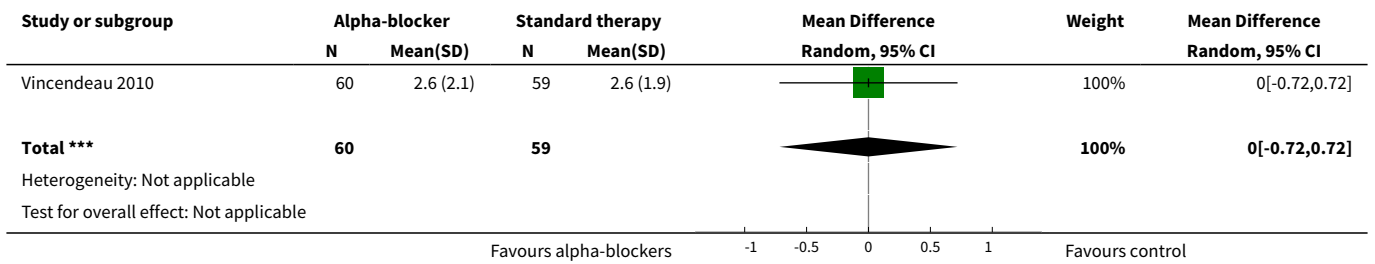
Analysis 6.2. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 2 Major adverse events.



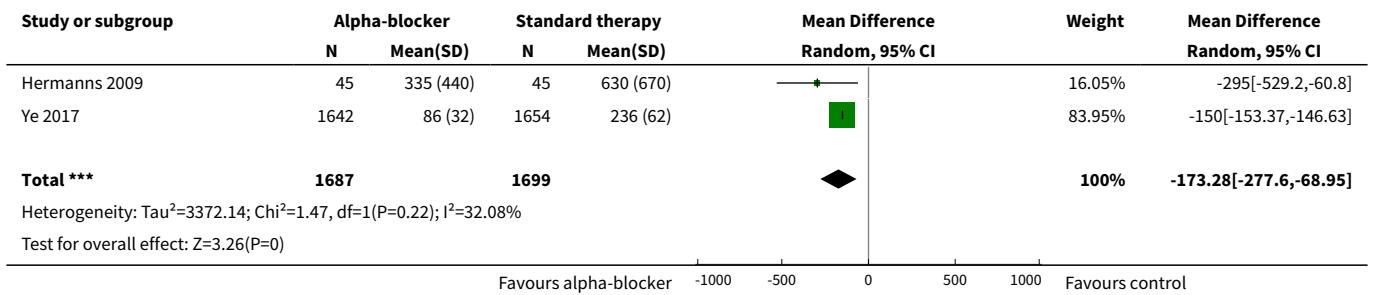
Analysis 6.3. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 3 Stone expulsion time.



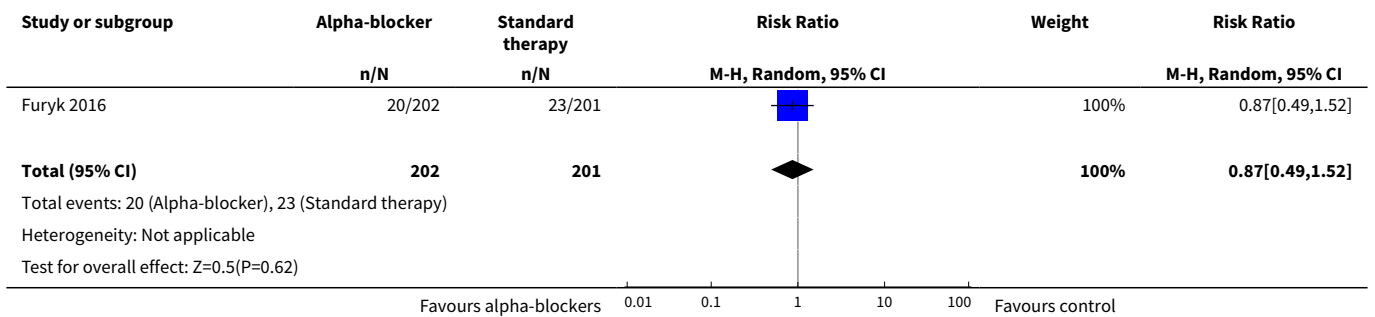
Analysis 6.4. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 4 Pain episodes.



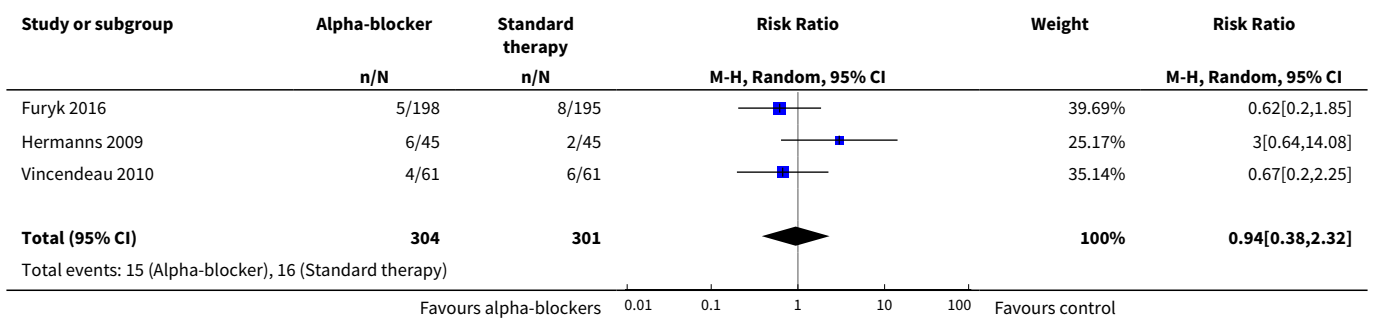
Analysis 6.5. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 5 Dose of diclofenac.

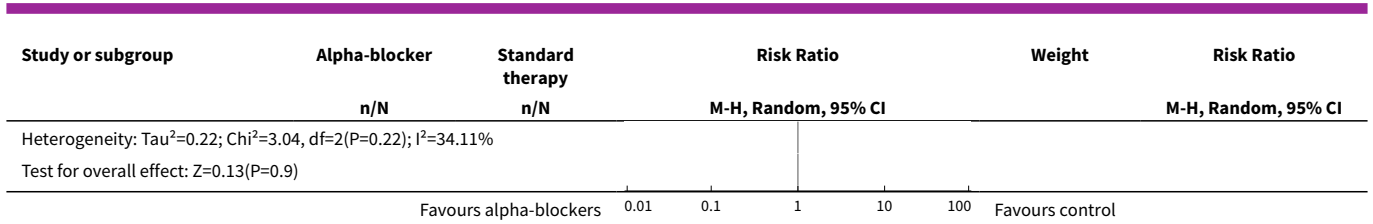


Analysis 6.6. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 6 Hospitalisation.



Analysis 6.7. Comparison 6 Sensitivity analysis 2: high-quality studies, Outcome 7 Surgical intervention.





APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Ureterolithiasis explode all trees 2. MeSH descriptor Ureteral Obstruction, this term only 3. MeSH descriptor Colic, this term only 4. (ureterolithiasis):ti,ab,kw in Clinical Trials 5. (ureteral colic*):ti,ab,kw or (ureteral stone*):ti,ab,kw or (ureteral calcul*):ti,ab,kw in Clinical Trials 6. (1 OR 2 OR 3 OR 4 OR 5) 7. MeSH descriptor Adrenergic alpha-Antagonists explode all trees 8. tamsulosin* or doxazosin* or alfuzosin* or terazosin* or silodosin*:ti,ab,kw in Clinical Trials 9. (alpha blocker* or alpha-blocker*):ti,ab,kw in Clinical Trials 10.(7 OR 8 OR 9) 11.(6 AND 10)
MEDLINE	<ol style="list-style-type: none"> 1. exp Ureterolithiasis/ 2. Ureteral Obstruction/ 3. Colic/ 4. ureterolithiasis.tw. 5. (ureter\$ adj3 (stone\$ or calcul\$ or colic)).tw. 6. or/1-5 7. exp Adrenergic alpha-Antagonists/ 8. alpha blocker\$.tw. 9. alpha receptor antagonist\$.tw. 10.exp Prazosin/ 11.tamsulosin.tw. 12.doxazosin\$.tw. 13.alfuzosin.tw. 14.terazosin.tw. 15.silodosin.tw. 16.or/7-15 17.and/6,16
Embase	<ol style="list-style-type: none"> 1. Ureter Stone/ 2. Ureter Obstruction/ 3. ureterolithiasis.tw. 4. (ureter\$ adj3 (stone\$ or calcul\$ or colic)).tw. 5. kidney colic/ or kidney pain/ 6. or/1-5

(Continued)

7. exp Alpha Adrenergic Receptor Blocking Agent/
8. alpha blocker\$.tw.
9. tamsulosin\$.tw.
10. doxazosin\$.tw.
11. alfuzosin.tw.
12. terazosin.tw.
13. silodosin.tw.
14. or/7-13
15. and/6,14

ClinicalTrials.gov	1. (Alpha-blocker OR tamsulosin OR alfuzosin OR silodosin OR doxazosin OR naftopidil OR terazosin) AND (stone OR ureter OR calculus OR calculi)
Conference proceedings	<ol style="list-style-type: none"> 1. Proceedings of major (mainly renal and stone-disease) conferences from 2005 to March 2016 2. EAU (European Association of Urology) 3. AUA (American Urological Association) 4. ESD (Experts in Stone Disease) 5. WCE (World Congress of Endourology) 6. SIU (Société Internationale d'Urologie)

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomization method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomization; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomization stated but no information on method used is available.</p>

(Continued)

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Low risk of bias: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Low risk of bias: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data.

Low risk of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse event); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

(Continued)

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
18 November 2017	New search has been performed	In this update we have added 35 new studies. GRADE approach has been applied to assess the quality of evidence.
18 November 2017	New citation required and conclusions have changed	In this update we have added 35 new studies. GRADE approach has been applied to assess the quality of evidence. The conclusion of the review has changed.

HISTORY

Protocol first published: Issue 5, 2010

Review first published: Issue 4, 2014

Date	Event	Description
2 April 2014	Amended	First published
9 July 2012	New search has been performed	Assessed as up-to-date

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: XZ, TL.
- Select studies: TC, XZ.
- Extract data from studies: TC, XZ, RV.
- Enter data into RevMan: TC, XZ, RV.
- Carry out the analysis: TC, XZ, RV.
- Interpret the analysis: TC, XZ, RV.
- Draft the final review: TC, XZ, TL.
- Resolve disagreements: TL.
- Update the review: TC, XZ, RV, TL.

DECLARATIONS OF INTEREST

Thijs Campschroer: none.

Xiaoye Zhu: none.

Robin WM Vernooij: none.

MTW Tycho Lock: none.

SOURCES OF SUPPORT

Internal sources

- Department of Urology, Rijnstate, Arnhem, Netherlands.
- Department of Urology, University Medical Center Utrecht, Utrecht, Netherlands.
- Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This Review is based on a published protocol ([Zhu 2010](#)). It provides an update of the published review ([Campschroer 2014](#)).

Major differences between the previous review and the update include the following.

- 'Major adverse events' has been added as a co-primary outcome.
- Need for surgical intervention has been added as a secondary outcome.
- The comparison of alpha-blockers versus calcium channel blockers has been omitted in light of readability and clinical applicability.
- A new type of alpha-blocker (silodosin) has been added as an intervention.
- GRADE approach has been applied to assess the quality of evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Antagonists [adverse effects] [*therapeutic use]; Analgesics [therapeutic use]; Diclofenac [therapeutic use]; Hospitalization [statistics & numerical data]; Randomized Controlled Trials as Topic; Time Factors; Ureteral Calculi [diagnostic imaging] [*drug therapy]

MeSH check words

Adult; Humans