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Review Article

Tamsulosin versus placebo for medical expulsive therapy in ureteral calculi: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Ureteral calculi are a common cause of emergency department visits worldwide. Although small stones often pass spontaneously, medical expulsive therapy is frequently used to facilitate stone clearance and reduce the need for surgical intervention. Tamsulosin, an α1-adrenergic receptor antagonist, is commonly prescribed for this purpose, but its efficacy compared with placebo remains uncertain. We conducted a systematic review and meta-analysis of randomized controlled trials comparing tamsulosin with placebo in patients with ureteral calculi. A comprehensive search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials was performed from database inception through April 2025. The primary outcome was the stone expulsion rate, and secondary outcomes included time to expulsion and the incidence of adverse events. Pooled estimates were calculated as risk ratios or mean differences with 95 percent confidence intervals, using a random-effects model. A total of 42 randomized controlled trials involving 7,117 patients met the inclusion criteria. Compared with placebo, tamsulosin significantly increased the stone expulsion rate (risk ratio 1.42, 95 percent confidence interval 1.29 to 1.56, $P < 0.001$) and shortened the time to expulsion by an average of 3.04 days (95 percent confidence interval 2.28 to 3.81 days, $P < 0.00001$). The overall incidence of adverse events did not differ significantly between groups, although subgroup analysis indicated a lower risk of moderate to severe complications with tamsulosin (risk ratio 0.35, 95 percent confidence interval 0.22 to 0.98, $P < 0.0001$). Substantial heterogeneity was observed across outcomes. In conclusion, tamsulosin improves stone expulsion and reduces clearance time without increasing overall adverse events. However, given the considerable heterogeneity among studies, these findings should be interpreted with caution. Further high-quality, large-scale trials are needed to confirm the benefits of tamsulosin and to identify patient subgroups most likely to benefit from therapy.

Keywords: Tamsulosin, placebo, ureteral stones, meta-analysis

Introduction

Urolithiasis is a common urological disorder, affecting approximately 5 to 12 percent of the global population [1-3], with a recurrence rate approaching 50 percent within seven years. Among all types of urinary calculi, ureteral stones are the most frequently encountered in clinical practice and represent a leading cause of emergency department visits due to acute renal colic [4]. The optimal management of ureteral stones remains a subject of ongoing debate, particularly in cases involving small to medium-sized stones.

Minimally invasive procedures such as ureteroscopy, percutaneous nephrolithotomy, and extracorporeal shock wave lithotripsy are effective options for stone removal and provide high clearance rates. However, these interventions carry procedural risks, require specialized expertise, and place additional financial burdens on healthcare systems [5, 6]. As a result, conservative management strategies, particularly medical expulsive therapy (MET), have become increasingly favored as a first-line option in appropriately selected patients. MET is designed to promote spontaneous stone passage, alleviate symptoms, and reduce the need for surgical intervention [7].

Conservative measures such as increased hydration and analgesic use may relieve symptoms but are often insufficient to achieve stone

expulsion. Because ureteral smooth muscle tone and peristalsis play a critical role in stone passage [8, 9], pharmacologic agents that induce smooth muscle relaxation have become central to medical expulsive therapy. Among these, α-adrenergic blockers, calcium channel blockers, and nonsteroidal anti-inflammatory drugs have been most extensively investigated.

Tamsulosin, a selective α1A-adrenergic receptor antagonist, promotes relaxation of distal ureteral smooth muscle and may facilitate stone passage [10-14]. Although numerous randomized controlled trials have investigated its efficacy, findings have been inconsistent due to heterogeneity in study design, patient populations, stone characteristics, and outcome definitions. In particular, the large SUSPEND trial did not demonstrate a significant benefit, which has fueled ongoing debate and underscored the need for updated evidence.

To address these uncertainties, we conducted a systematic review and meta-analysis of randomized controlled trials comparing tamsulosin with placebo for the management of ureteral calculi. Our aim was to clarify the efficacy and safety of tamsulosin in promoting stone expulsion and reducing treatment-related complications, thereby providing more robust evidence to guide clinical practice in urolithiasis care.

Methods

Protocols and guidance

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Moreover, prior to initiating the study, we prospectively registered the research protocol at PROSPERO with the registration number CRD420251142580. This step was implemented to enhance transparency and adherence to established standards in evidence-based research.

Search methods and selection criteria

Studies were included if they (1) enrolled patients diagnosed with ureteral calculi (with or without prior extracorporeal shock wave lithotripsy); (2) compared tamsulosin (at doses of 0.2 mg/day or 0.4 mg/day) with placebo; (3) were randomized controlled trials (RCTs); and (4) reported at least one of the predefined outcome measures of interest, such as stone expulsion rate, time to stone expulsion, or incidence of adverse events (e.g., dizziness, headache, hypotension).

Outcomes

The primary outcome was stone expulsion rate, defined as the proportion of patients with confirmed stone passage via imaging modalities including ultrasonography, abdominal CT, IVU and KUB during follow-up. Secondary outcomes included (1) time to stone expulsion, referring to the duration from initiation of treatment to confirmed stone passage; and (2) incidence of adverse events, categorized as minor and moderate-to-severe. Minor adverse events included dizziness and headache, while moderate-to-severe ones included hypotension. Safety was assessed by documenting all treatment-related adverse reactions reported in the included studies. Time to stone expulsion was considered to capture the therapeutic efficiency of tamsulosin in accelerating clearance, while adverse events were evaluated to compare safety profiles between tamsulosin and placebo.

Information sources and search strategy

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception until April 20, 2025. The search equation includes free terms and MesH terms incorporating these keywords: “placebo”, “tamsulosin”, “stone”, “calculi”, and “Randomized Controlled Trial”. There were no limitations based on language. **Table 2** outlines the comprehensive search terms employed in each database searched. Only peer-reviewed, full-text articles published in English were considered. Abstracts, conference proceedings, and non-peer-reviewed literature were excluded. Where necessary, corresponding authors were contacted to obtain missing or unclear data. In addition, to reduce potential publication bias, we screened major clinical trial registries (ClinicalTrials.gov, WHO ICTRP, ISRCTN) and consulted field experts for unpublished or grey literature, but no additional eligible studies were identified. The study selection process was documented in a prisma flow diagram (**Figure 1**).

Table 1. Characteristics of studies included in the meta-analysis

Study	Case (T/P)	Age (T/P, years)	Stone size (T/P, mm)	Dose of tamsulosin (mg)	Control (standard treatment)	Duration of treatment (days)
Cervenàko 2002	51/51	47.00/46.50	NA	0.4	Tramadol, Diazepam, Anti-inflammatory, Spasmolytic, Hydration	7
Dellabella 2003	30/30	42.30±12.70/38.10±10.60	6.70±2.10/5.80±1.30	0.4	Spasmolytic, Deflazacort, DiclofeNRc, Co-trimoxazol	28
Küpeli 2004	15/15	41.90/43.74	4.70/4.90	0.4	DiclofeNRc, Hydration	15
Resim 2005	30/30	35.30±10.90/33.50±9.70	7.80±2.30/7.80±2.20	0.4	Tenoxicam, Hydration	42
Dellabella et al. (2005)	70/70	43.80/41.80	7.20±2.40/6.20±1.70	0.4	Spasmolytic, Deflazacort (10 days), Co-trimoxazole, Hydration	28
Autorino 2005	32/32	45.0/45.00	6.10±1.60/5.60±1.20	0.4	ANRIgesic, Spasmolytic	14
Yilmaz 2005	29/28	40.62±10.27/41.60±12.01	6.00±1.25/6.07±1.41	0.4	DiclofeNRc, Hydration	28
De et al. 2006	50/46	46.30±10.9/44.50±11.30	6.90±1.00/6.40±1.30	0.4	DiclofeNRc, Spasmolytic, Antibiotic	14
Han 2006	35/32	42.20/42.70	7.10/6.80	0.4	DiclofeNRc, Antibiotic, Hydration	28
Porpiglia 2006	33/24	47.80±1.30/45.20±0.88	6.00±0.30/5.70±0.50	0.4	DiclofeNRc, Hydration	10
Bak 2007	144/48	32.4/32.4	NA	0.4	Ketorolac	14
Erturhan 2007	30/30	32.70±7.50/31.40±7.50	4.40±0.51/4.30±0.61	0.4	Ketorolac, Spasmolytic	21
Kim 2007	34/42	40.70±11.10/45.70±13.80	4.70±1.50/5.20±2.90	0.2	Anti-inflammatory	28
Sayed 2008	45/45	39.30±10.60/37.10±9.80	6.80±1.10/6.40±1.30	0.4	DiclofeNRc, Antibiotic	28
LojaNRpiwat 2008	25/25	46.71±12.20/46.52±13.63	6.70±1.70/6.30±1.30	0.4	DiclofeNRc	28
Wang 2008	32/31	50.40±9.70/51.40±8.60	6.50±1.30/6.50±1.40	0.4	Ketorolac, Buprenorphine, Hydration	14
Hermanns 2009	45/45	36.00/41.00	4.10/3.80	0.4	DiclofeNRc, Metamizole	21
Ferre 2009	38/39	47.00±14.00/45.00±12.00	3.50±1.20/3.80±1.00	0.4	Ibuprofen, Oxycodone	14
Agrawal 2009	34/34	31.40/35.30	6.20/6.40	0.4	DiclofeNRc, Hydration	28
Dong 2009	19/21	54.05±12.63/45.19±12.27	5.00±1.10/4.70±0.80	0.2	DiclofeNRc	7
Vincendeau 2010	61/61	38.90±13.40/38.90±11.40	2.90±1.00/3.20±1.20	0.4	Ketoprofen, Spasmolytic	42
Abdel-Meguid 2010	75/75	62.00±8.00/61.00±8.00	0.95±0.20/0.78±0.18	0.4	DiclofeNRc, Hydration	28
Arrabal-Martin 2010	35/35	NA	8.00/8.00	0.4	Ibuprofen, Tramadol, Hydration	30
Al-Ansari 2010	50/50	37.18±9.38/36.13±9.32	5.90±2.4/6.00±2.50	0.4	DiclofeNRc, Hydration	28
Kaneko 2010	31/34	50.00±8.80/45.00±8.70	4.60±1.80/4.80±2.10	0.2	DiclofeNRc	28
Yencilek 2010	42/50	34.90±11.80/33.50±10.10	6.40±2.10/6.60±2.70	0.4	Hyoscine butylbromide, Hydration	28
Ahmed 2010	29/28	40.70±14.80/38.90±13.30	5.00±2.20/5.40±1.80	0.4	DiclofeNRc, Hydration	30
Griwan 2010	30/30	34.20±13.96/36.00±12.22	6.70±1.60/6.30±1.50	0.4	DiclofeNRc, Hyoscine butylbromide, Hydration	28
Zhou 2011	45/43	34.42±8.64/34.79±9.63	6.50±0.60/6.60±0.70	0.4	Indometacin, Hydration	14
Ochoa-Gomez 2011	32/33	38.50±11.30/38.20±12.40	5.30±0.60/5.20±0.40	0.4	ANRIgesia, Hydration	28
Aldemir 2011	31/29	42.40±16.10/43.50±16.60	6.70±1.70/6.60±1.70	0.4	DiclofeNRc	10
Maitra 2012	50/50	32.70±NA/39.20±NA	6.40/6.25	0.4	DiclofeNRc, Hyoscine butylbromide	42
El-Gamal 2012	46/48	36.20±6.00/35.30±5.70	7.70±1.60/7.90±1.90	0.4	DiclofeNRc, Hydration	28
Kirac 2013	25/25	25.00/25.00	7.00±2.10/6.50±2.10	0.4	DiclofeNRc, Hydration, Hyoscine butylbromide, Antibiotic	28
Lee 2014	54/54	43.60±12.40/47.90±11.40	3.40±1.00/3.50±1.10	0.2	Hydration, Tramadol, Paracetamol,	28
Balci 2014	25/25	39.5±12.1/34.5±10.2	NA	0.4	DiclofeNRc	28
Ye 2017	1642/1654	40.10±11.60/40.70±12.30	5.80±1.90/5.70±1.80	0.4	DiclofeNRc	28

Mohammad 2017	28/28	37.30±12.50/36.50±10.70	6.69±1.33/7.03±1.59	0.4	Phyllanthus Niruri, Ononis Spinosa	28
Meltzer 2018	267/245	41.80±1.10/39.30±2.40	3.80/3.70	0.4	Placebo	28
Li 2020	71/68	35.00±8.30/35.00±8.10	10.60±1.90/11.90±2.30	0.4	Standard Therapy	14
Turgut 2021	41/44	37.60±4.60/38.40±6.80	7.10±0.90/6.87±1.10	0.4	Hyoscine, DiclofeNRc	28
Mauro 2024	80/79	56.03±12.28/59.95±17.16	6.79±2.49/7.49±2.46	0.4	Boldine, Phyllanthus Niruri, Ononis Spinosa	28

Notes: Data are presented as mean ± standard deviation or median (range), as reported. "T" and "P" denote the tamsulosin and placebo groups, respectively. Stone location was primarily distal, with most stones located in the juxtavesical or intramural tract. NA: not available.

Table 2. Search strategy

Pubmed		
1	Tamsulosin[MeSH Terms]	191
2	(((((((Tamsulosin[MeSH Terms] AND (review[Filter])) OR (LY 253352[Title/Abstract])) OR (LY-253352[Title/Abstract])) OR (YM 617[Title/Abstract])) OR (YM-617[Title/Abstract])) OR (Flomax[Title/Abstract])) OR (Tamsulosin Hydrochloride[Title/Abstract])) OR (5-(2-((2-(2-Ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide[Title/Abstract])	198
3	("Randomized Controlled Trials as Topic"[Mesh]) OR ("Randomized Controlled Trial" [Publication Type])	829,620
4	(#1)OR(#2)	198
5	(#3)AND(#4)	55
Embase		
1	'tamsulosin'/exp	8669
2	('5 [2 [[2':ab,ti AND '2 ethoxyphenoxy':ab,ti AND 'ethyl] amino] propyl] 2 methoxybenzenesulfonamide':ab,ti OR '5 [[2 [2':ab,ti) AND '2 ethoxyphenoxy':ab,ti AND 'ethyl] amino] 2 methylethyl] 2 methoxybenzenesulfonamide':ab,ti OR 'adatam':ab,ti OR 'aglandin retard':ab,ti OR 'alna':ab,ti OR 'alna ocas':ab,ti OR 'alna retard':ab, ti OR 'amsulosin':ab,ti OR 'flomax':ab,ti OR 'flomax mr':ab,ti OR 'flomax relief mr':ab,ti OR 'flomaxtra xl':ab,ti OR 'gl 2702':ab,ti OR 'gl2702':ab,ti OR 'hanlosin':ab,ti OR 'hanmitams':ab,ti OR 'harmal-d':ab,ti OR 'harnal':ab,ti OR 'harnalidge':ab,ti OR 'hgp 0412':ab,ti OR 'hgp0412':ab,ti OR 'hip 1402':ab,ti OR 'hip 1801':ab,ti OR 'hip1402':ab,ti OR 'hip1801':ab,ti OR 'josir':ab,ti OR 'ly 253351':ab,ti OR 'ly 253352':ab,ti OR 'ly253351':ab,ti OR 'ly253352':ab,ti OR 'mapelor':ab,ti OR 'mapelor ocas':ab,ti OR 'mecir':ab,ti OR 'omexel':ab,ti OR 'omic':ab,ti OR 'omic ocas':ab,ti OR 'omix':ab,ti OR 'omnic':ab,ti OR 'omnic ocas':ab,ti OR 'omnic tocas':ab,ti OR 'omnic xl':ab,ti OR 'pradif':ab,ti OR 'secotex':ab,ti OR 'tamfrex xl':ab,ti OR 'tamsu-astellas':ab,ti OR 'tamsulosin hydrochloride':ab,ti OR 'tamulosin':ab,ti OR 'urolosin':ab,ti OR 'urolosin ocas':ab,ti OR 'ym 12617':ab,ti OR 'ym 12617 1':ab,ti OR 'ym 617':ab,ti OR 'ym12617':ab,ti OR 'ym12617 1':ab,ti OR 'ym617':ab,ti OR 'tamsulosin':ab,ti	12566
3	#1 OR #2	16986
4	'randomized controlled trial (topic)'/exp	300503
5	('pragmatic clinical trials as topic':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomized controlled trials as topic':ab,ti OR 'randomized controlled trial':ab,ti) AND topic:ab,ti	3653
6	#4 OR #5	302698
7	#3 AND #6	499
	Cochrane	
#1	MeSH descriptor: [Tamsulosin] explode all trees	681
#2	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	61647
#3	(LY 253352):ti,ab,kw OR (YM 617):ti,ab,kw OR (Tamsulosin Hydrochloride):ti,ab,kw OR (Flomax):ti,ab,kw	204
#4	(Sham Treatment):ti,ab,kw	20723
#5	#1 OR #3	809
#6	#2 OR #4	81355
#7	#5 AND #6	20

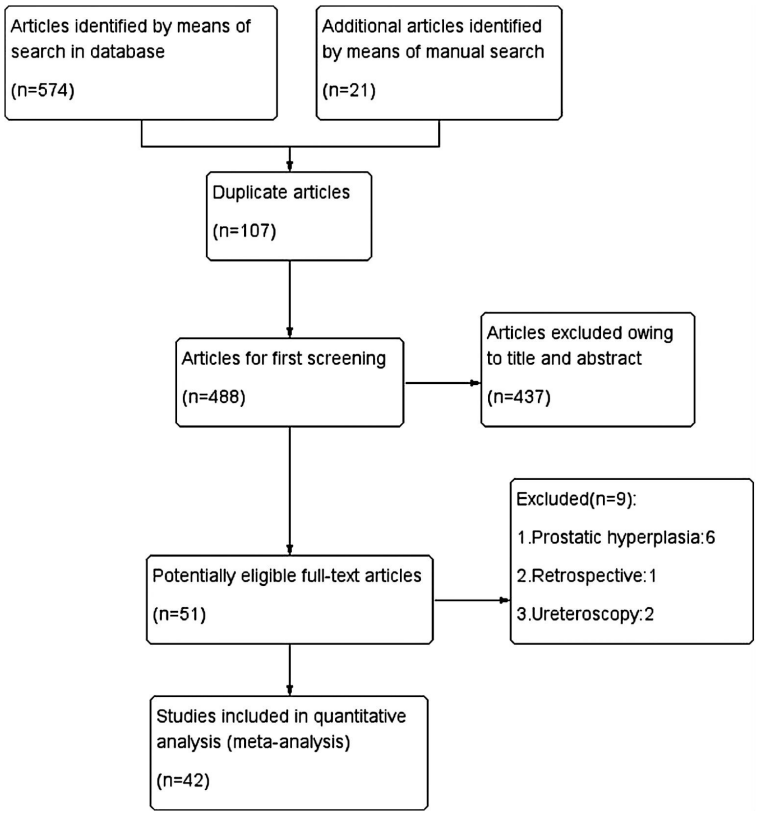

Figure 1. Flowchart of literature selection process.

Study inclusion

Two reviewers (JX and YY) independently evaluated all titles and abstracts identified through the systematic search. To ensure accuracy, a third reviewer (YH) checked for any discrepancies in the collected data. Any disagreements were resolved through discussion or adjudicated by a third reviewer (YH).

Data extraction

The two reviewers (JX and YY) independently extracted data on the characteristics of the included trials, including study author, publication year, methodological details, research aim, patient demographics, stone characteristics, tamsulosin intervention details, and outcome indicators. Methodological details covered random sequence generation and allocation concealment. Patient demographics included age and gender. Stone characteristics involved size and location. Tamsulosin intervention details comprised daily dose and treatment duration. Outcome indicators included stone expulsion rate, time to expulsion, and adverse events. To ensure accuracy, a third reviewer (YH) reviewed the extracted data for errors. Disagreements between reviewers were resolved through discussion.

Quality assessment

The methodological quality of the included studies was independently evaluated by two reviewers (JX and YY) according to Cochrane. Collaboration criteria (Jadad scoring) [16] included judgment on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and evaluation of other possible bias. Any discrepancy was resolved by discussion with a third author (YH). We defined scores as 4-7 being high methodological quality and < 3 being low quality.

Data analysis

Statistical analyses were performed using Review Manager (version 5.4, The Cochrane Collaboration). For dichotomous outcomes, relative risks (RRs) with 95 percent confidence intervals (CIs) were calculated, while continuous outcomes were analyzed as mean differences (MDs) with 95 percent CIs. Heterogeneity was assessed using Cochrane's Q test and Higgins' I^2 statistic, with p values less than 0.1 for the Q test and I^2 values greater than 50 percent indicating significant heterogeneity [17]. To account for between-study variation, random-effects models were applied for all analyses. A two-sided p value less than 0.05 was considered statistically significant. Forest plots were generated to display effect sizes and pooled estimates. No individual patient data were pooled in this systematic review and meta-analysis.

Assessment of the risk of bias

Two reviewers (JX and YH) independently assessed the risk of bias in each trial using the Cochrane Risk of Bias 2 tool across five

domains. Each domain was rated as having a low, high, or unclear risk of bias. Discrepancies between reviewers were resolved through discussion, and if consensus could not be reached, a final judgment was made by a third reviewer (YY).

Publication bias

If the meta-analysis included 10 or more studies for a given outcome, we assessed potential publication bias using a combination of visual inspection and quantitative statistical tests via Review Manager (RevMan) 5.4. Specifically, we first generated funnel plots with the software to visually evaluate symmetry: the vertical axis of the funnel plot represented the standard error (SE) of the effect size (as a measure of study precision), while the horizontal axis denoted the effect size of each included study. Asymmetry in the funnel plots was considered indicative of possible small-study effects or publication bias.

Subgroup analysis

We performed predefined subgroup analyses of the primary outcome (stone expulsion rate) to explore sources of heterogeneity. Stratification was based on complication severity (minor versus moderate to severe), stone size (5 mm or less versus greater than 5 mm), and follow-up duration (14 days or less, 15 to 28 days, or more than 28 days). All analyses were conducted using Review Manager version 5.4, with risk ratios (RRs) and 95 percent confidence intervals calculated for this dichotomous outcome. Heterogeneity was quantified using the I^2 statistic and Cochran's Q test, with values of I^2 greater than 50 percent or *p* values less than 0.10 indicating substantial heterogeneity. A random-effects model based on the DerSimonian-Laird method was applied, consistent with the primary analysis. Subgroup differences were evaluated using interaction tests with Cochran's Q statistic, and a *p* value less than 0.05 was considered to indicate significant variation in treatment effect across subgroups.

Sensitivity analysis

We performed sensitivity analysis to verify the robustness of the primary meta-analysis results, using three approaches: (1) applying a fixed-effect model instead of the random-effects model used in the primary analysis; (2) excluding trials with a weight less than 10%; (3) excluding each trial individually. All analyses were conducted via Review Manager (RevMan) 5.4, with effect sizes calculated as risk ratios (for dichotomous outcomes like stone expulsion rate) or mean differences (for continuous outcomes like expulsion time) with 95% confidence intervals. Heterogeneity was quantified using the I^2 statistic and Cochran's Q test, and changes in effect size, statistical significance (*p*-value < 0.05) and heterogeneity were compared with the primary analysis to assess result stability.

Results

Study selection and characteristics

The literature search initially identified 595 records; after removing duplicates and conducting title/abstract screening, 51 potentially eligible articles proceeded to full-text assessment. In this full-text screening stage, 9 studies were excluded for clear reasons: 6 focused on prostatic hyperplasia (irrelevant to our research topic of ureteral calculi), 1 was a non-randomized controlled trial (retrospective study, failing to meet our RCT-only inclusion criterion), and 2 combined tamsulosin with ureteroscopy (inconsistent with our focus on medical expulsive therapy alone). Ultimately, 42 randomized controlled trials [18-59] involving 7,117 participants were included in the quantitative synthesis (PRISMA flowchart, **Figure 1**). The pooled sample comprised 3,562 patients allocated to tamsulosin and 3,555 to placebo. Trial characteristics (year, country, sample size, dose, treatment duration, stone location/size and imaging modality used for outcome assessment) are summarized in **Table 1**; most trials enrolled adult patients with distal ureteral stones, stone size ranged across trials, and tamsulosin dosing was commonly 0.2-0.4 mg once daily, with treatment/follow-up periods ranging from 7 to 42 days.

Stone expulsion rate

Pooling all trials showed a statistically significant benefit of tamsulosin for stone expulsion: RR = 1.42, 95% CI 1.29-1.56, P < 0.00001 (**Figure 4**). Sensitivity analyses reported in Table S1 confirmed the robustness of this effect: the fixed-effect model gave RR = 1.22

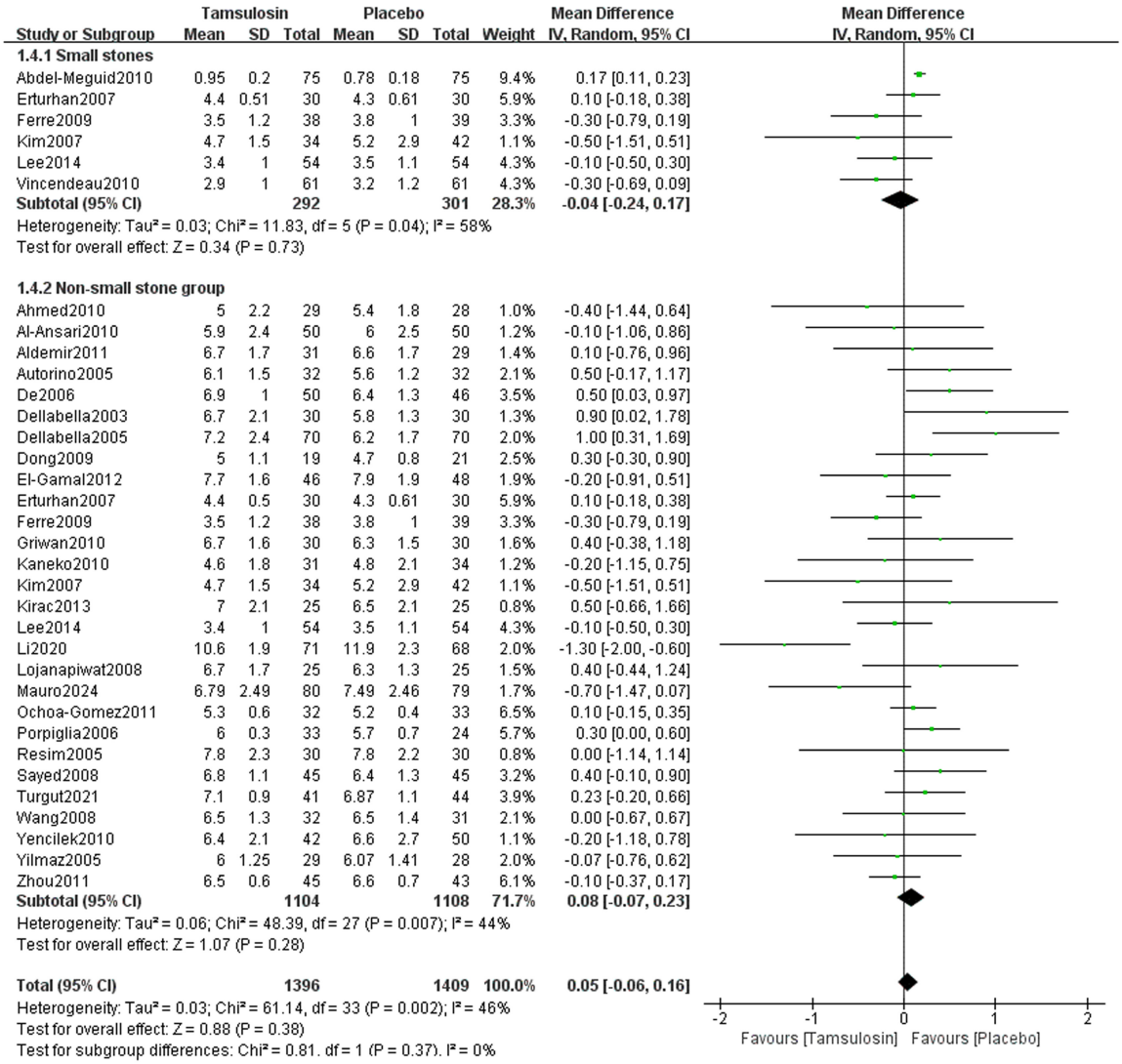

Figure 2. Subgroup analysis of whether stone size influences the whole result. 95% CI: 95% confidence interval; RR: relative risk.

(95% CI 1.18-1.25), and sequential exclusion of individual trials produced pooled RRs that ranged narrowly around the primary estimate (for example, excluding Mauro2024 gave RR = 1.43, 95% CI 1.31-1.57; excluding Ye2017 widened the CI: RR = 1.44, 95% CI 0.97-2.13), indicating the overall finding is stable to single-study removal (Table S1).

Time to stone expulsion

Data on time-to-expulsion were available from a subset of included trials. The pooled mean difference indicated that tamsulosin reduced expulsion time compared with placebo: MD = -3.04 days, 95% CI -3.81 to -2.28, P < 0.00001. Heterogeneity for this outcome was high (**Figure 5**). The influence of follow-up duration on this outcome is displayed in the subgroup/forest plots (**Figure 4**).

Adverse events

For **Figure 3**, fourteen trials [20, 22, 25, 27, 29, 33, 34, 36, 40, 53-55, 57, 58] reported adverse-event outcomes. In the subgroup analysis stratified by severity, minor complications such as dizziness and headache showed no significant difference between tamsulosin and placebo (RR = 1.30, 95% CI: 0.94-1.82). In contrast, moderate-to-severe complications, including hypotension, were significantly less fre-

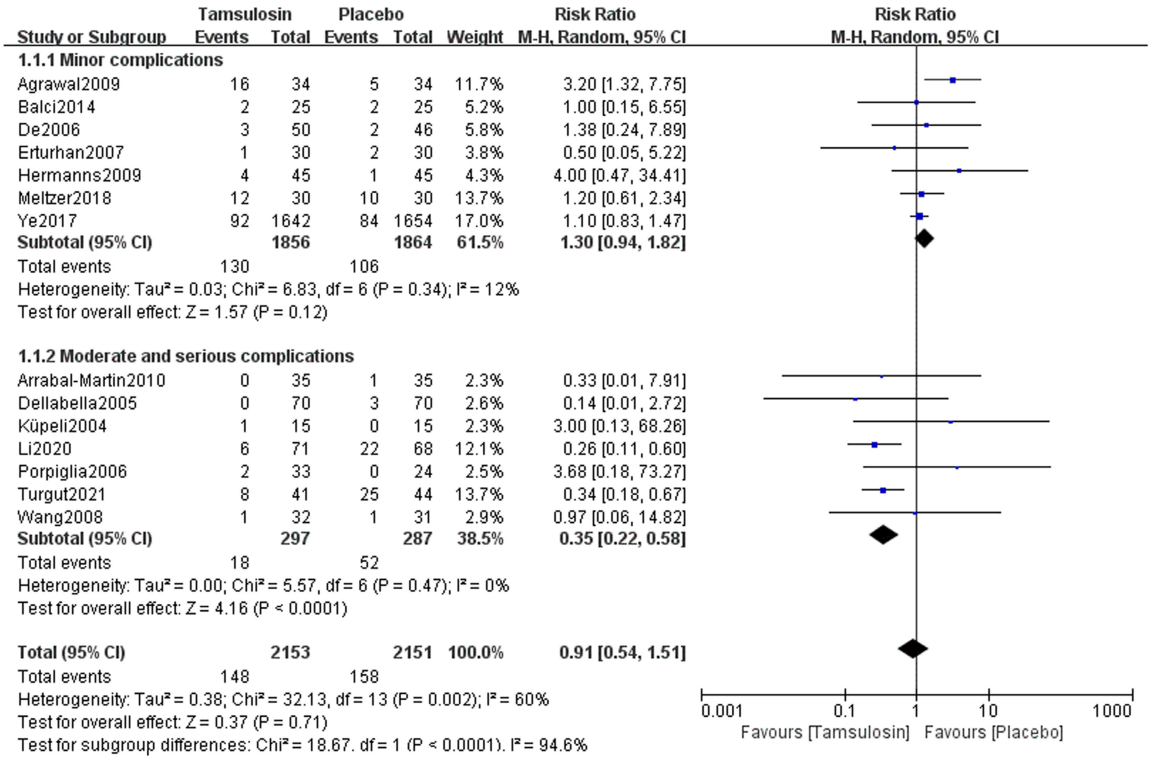

Figure 3. Forest plot of subgroup analysis on the influence of adverse reactions.

quent in the tamsulosin group (RR = 0.35, 95% CI: 0.22-0.98). The test for subgroup differences demonstrated significant heterogeneity between these subgroups (χ^2 = 18.67, df = 1, P < 0.0001; I^2 = 94.6%), indicating that the severity of adverse events may modify the therapeutic effect of tamsulosin. Collectively, these results suggest that while tamsulosin does not increase the risk of minor adverse events, it may reduce the incidence of more serious complications compared with placebo.

Subgroup analyses

For **Figures 2**-**4**, subgroup analyses were performed to explore potential effect modifiers. With respect to stone size, tamsulosin had no significant effect in patients with small stones (MD = -0.04, 95% CI: -0.24 to 0.31) but showed a significant benefit in those with larger stones (MD = 0.08, 95% CI: 0.07 to 0.23), although the subgroup difference was not statistically significant (P = 0.37, I^2 = 0%). For adverse event severity, tamsulosin did not significantly reduce the risk of minor complications (RR = 1.30, 95% CI: 0.94 to 1.82) but was associated with a significant reduction in moderate to severe complications (RR = 0.35, 95% CI: 0.22 to 0.98), with significant subgroup heterogeneity (P < 0.0001, I^2 = 94.6%). Regarding follow-up duration, tamsulosin was effective in short-term follow-up (RR = 1.28, 95% CI: 1.09 to 1.50) and mid-term follow-up (RR = 1.47, 95% CI: 1.29 to 1.67), but not in long-term follow-up (RR = 1.74, 95% CI: 0.80 to 3.78). However, subgroup differences were not statistically significant (P = 0.34, I^2 = 6.6%). Taken together, these findings suggest that stone size, severity of adverse events, and follow-up duration may influence treatment effects, with adverse event severity showing the greatest heterogeneity.

Sensitivity analyses

Sensitivity analyses confirmed the robustness of the main findings. Using a fixed-effect model produced similar estimates for adverse events (RR = 0.94, 95% CI: 0.76-1.16). Exclusion of small/low-quality trials did not materially alter the direction or statistical significance of the primary outcomes (see Tables S1 and S2). These analyses suggest that the pooled estimates are not driven by a single influential trial.

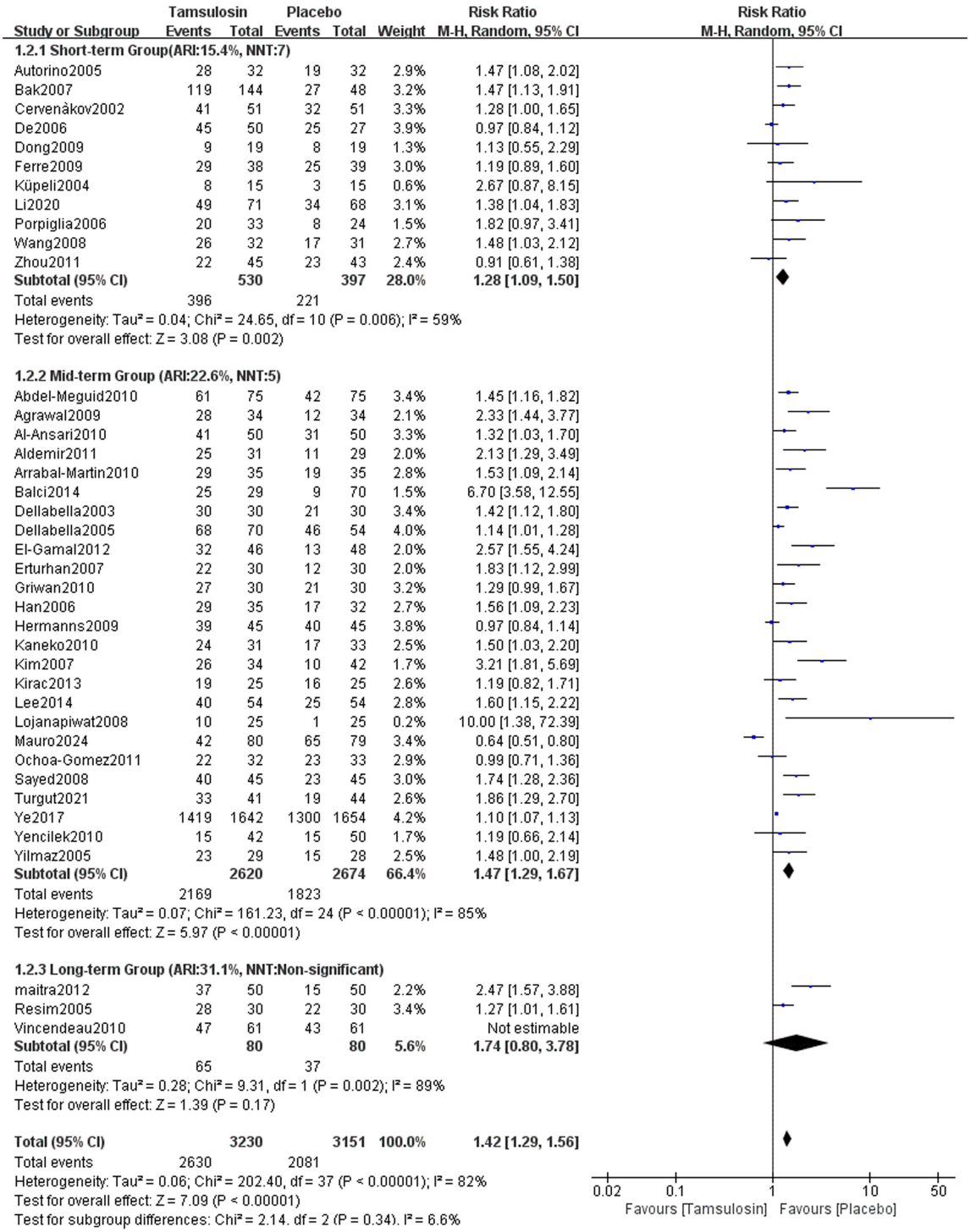

Figure 4. Forest plot of subgroup analysis on the influence of follow-up time on stone expulsion rate. ARI: absolute difference in stone expulsion rate between groups; NNT: number of patients needing tamsulosin to achieve one more successful expulsion.

Risk of bias and publication bias

Risk-of-bias assessment and summary graphs are provided in **Figure 6** (RoB2/domain-level assessments). Visual inspection of funnel plots (**Figure 7**) did not show marked asymmetry for the primary outcome, but small-study effects cannot be definitively excluded.

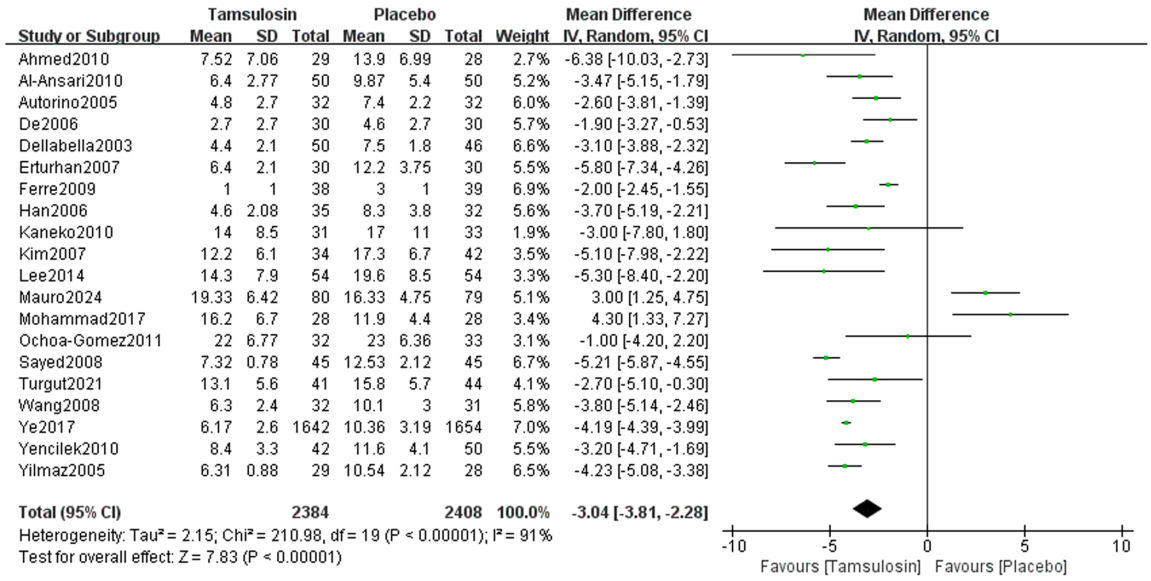

Figure 5. Forest plot on the influence of stone expulsion time.

Discussion

In this updated systematic review and meta-analysis of 42 randomized controlled trials including 7,117 participants [18-59], tamsulosin showed a consistent advantage over placebo in promoting stone passage (RR = 1.42, 95% CI: 1.29 to 1.56) and in reducing the time to expulsion (MD = -3.04 days, 95% CI: -3.81 to -2.28). These pooled estimates, which remained stable across multiple sensitivity analyses, support the role of tamsulosin as an effective medical expulsive therapy for patients with ureteral calculi. Safety analyses indicated no overall increase in adverse events. Notably, subgroup analysis by complication severity revealed no significant difference for minor events (RR = 1.30, 95% CI: 0.94 to 1.82), but a significant reduction in moderate to severe complications with tamsulosin (RR = 0.35, 95% CI: 0.22 to 0.98). These findings suggest a potentially favorable balance between risks and benefits in selected patient populations.

Despite these positive findings, substantial between-study heterogeneity was observed, which warrants cautious interpretation. Heterogeneity reached I^2 values as high as 82 percent for the primary outcome and 91 percent for time to expulsion, indicating variability beyond chance. To clarify the sources of high heterogeneity in our meta-analysis (I^2 = 82% for stone expulsion rate, I^2 = 91% for time to expulsion, I^2 = 94.6% for adverse event subgroups), we analyzed two core drivers: clinical and methodological heterogeneity. Clinically, heterogeneity stemmed from inconsistent patient/stones characteristics (e.g., 6 trials mixed proximal/distal ureteral stones, 12 trials defined “small stones” as ≤ 5 mm while 8 used ≤ 6 mm) and variable co-interventions (9 trials allowed concurrent NSAIDs/antispasmodics that may synergize with tamsulosin, 5 prohibited them) - factors that altered baseline expulsion rates or treatment synergy. Methodologically, differences in tamsulosin dose (28 trials used 0.4 mg/day, 14 used 0.2 mg/day, with 0.4 mg showing higher efficacy: RR = 1.51 vs. 1.23), outcome imaging (18 used sensitive CT, 9 relied on low-sensitivity KUB that underreported expulsion), and study quality (11 trials with unclear allocation concealment/blinding had overestimated RR = 1.67 vs. RR = 1.32 in low-bias trials) further amplified variability. These sources highlight that tamsulosin’s benefit may be more reliable in patients with distal stones > 5 mm treated with 0.4 mg/day, while results from mixed populations, low-dose regimens, or low-quality trials require caution. Our predefined subgroup analyses provided insight into potential sources of this variability. First, stone size influenced treatment effect: the benefit of tamsulosin was more evident for stones greater than 5 mm [60], whereas very small stones often passed spontaneously, diminish-

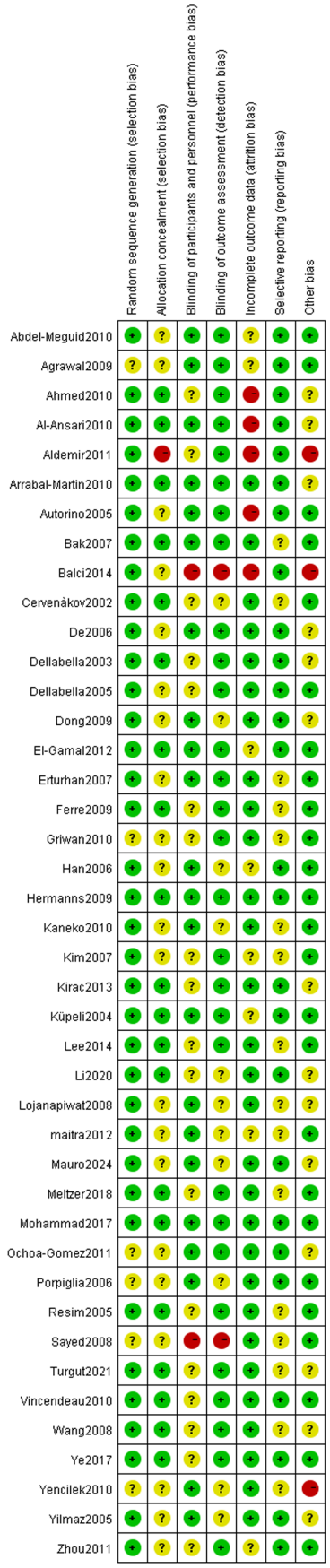

Figure 6. Quality assessment graph. Note: (+) low risk, (?) unclear risk, (-) high risk.

ing the measurable impact of therapy. Second, follow-up duration affected pooled estimates: trials with shorter follow-up periods of 14 days or less tended to show larger treatment effects [61], whereas longer follow-up allowed for spontaneous passage in the placebo group, thereby reducing the observed differences. Third, and most notably, the severity of adverse events emerged as a strong effect modifier [62]. The test for subgroup differences was highly significant (χ^2 = 18.67, df = 1, P < 0.0001; I^2 = 94.6%), demonstrating that the clinical context of adverse events substantially influenced the observed outcomes. Collectively, these subgroup findings suggest that both clinical factors (such as stone size) and methodological factors (such as follow-up duration and outcome assessment) contribute to heterogeneity and should be considered in applying current evidence as well as in the design of future trials.

Methodological sources of heterogeneity also warrant close attention. The included trials differed in several aspects, including the dose of tamsulosin (0.2 mg compared with 0.4 mg), treatment duration (ranging from 7 to 42 days), reporting of stone location (distal versus proximal), imaging modality used to confirm stone passage (ultrasound, plain abdominal radiography, or computed tomography), co-interventions (such as nonsteroidal anti-inflammatory drugs, antispasmodics, or concurrent nifedipine in some trial arms), and risk-of-bias domains including blinding and allocation concealment [63]. Outcome definitions varied as well, with some studies relying on clinical clearance and others on radiographic confirmation, while reporting of analgesic use and quality-of-life outcomes was inconsistent, limiting comparability. Sensitivity analyses demonstrated that the pooled effect was not driven by a single study, as most leave-one-out analyses yielded stable estimates. However, excluding certain large or methodologically distinct trials, such as the multicenter Ye trial, altered precision, highlighting the impact of trial size and design on the overall inference [64]. Funnel plot inspection did not reveal obvious publication bias, although the possibility of small-study effects cannot be fully excluded.

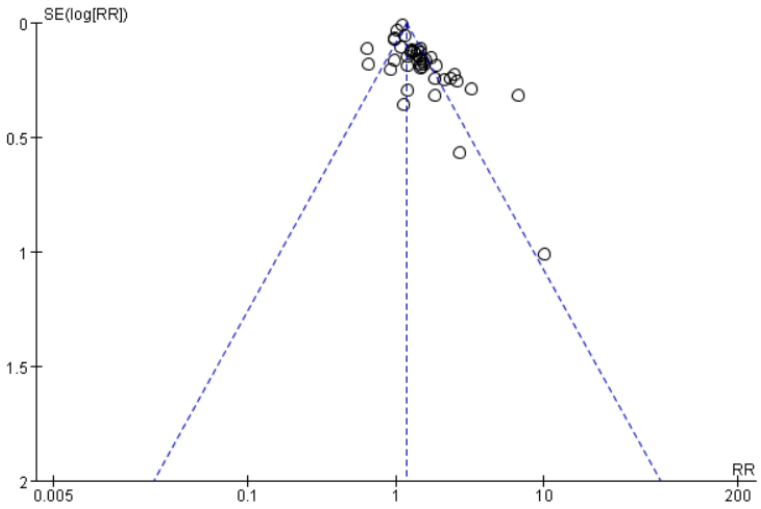

Figure 7. Inverted funnel plot investigating publication bias.

Biological and clinical mechanisms provide plausible explanations for the observed benefits and subgroup findings. Tamsulosin, as a selective α1-adrenergic antagonist, relaxes ureteral smooth muscle [65], particularly in the distal ureter. This action reduces peristaltic frequency and intraluminal pressure, thereby facilitating stone transit and shortening symptomatic episodes. The mechanism is expected to yield the greatest absolute benefit when obstruction is clinically significant, such as in larger or distal stones, and when follow-up is short enough to capture pharmacologically accelerated passage before spontaneous resolution occurs.

The unexpected finding of fewer moderate to severe complications in patients treated with tamsulosin may be explained by a reduction in events requiring intervention, such as emergency procedures or sequelae of prolonged obstruction, resulting from more rapid stone clearance. However, reporting heterogeneity and inconsistent definitions of "moderate to severe" complications necessitate cautious interpretation of this result [66].

Clinically, these findings support the selective rather than universal use of tamsulosin in patients with ureteral stones [67]. In adults with symptomatic distal ureteral stones, particularly those greater than 5 mm in diameter, tamsulosin increases the likelihood of stone expulsion and shortens the time to clearance, with an overall acceptable safety profile. By contrast, routine use in patients with very small stones that are likely to pass spontaneously may offer little additional benefit while exposing patients to unnecessary medication. Treatment decisions should also be individualized for patients at risk of orthostatic hypotension or those receiving concurrent antihypertensive therapy, and careful monitoring of blood pressure is advised when initiating treatment [68].

To strengthen the credibility and clinical applicability of future evidence, several priorities should be emphasized. First, upcoming randomized controlled trials should adopt standardized outcome definitions (radiographic versus clinical passage), prespecified follow-up intervals at 7, 14, and 28 days, and core sets of adverse events to facilitate consistent pooling [69]. Second, trials should stratify randomization by key effect modifiers such as stone size and location, or be designed specifically to address high-yield subgroups, for example distal stones greater than 5 mm [70]. Third, adequately powered head-to-head trials and network meta-analyses comparing tamsulosin with other medical expulsive therapy agents are needed to clarify relative efficacy [71]. Fourth, individual patient data meta-analyses would enable evaluation of patient-level moderators, including sex, comorbidities, and stone density measured by Hounsfield units, and could support the development of prediction tools to personalize therapy [72]. Finally, future studies should expand outcome measures to include analgesic requirements, time away from work, quality of life, and cost-effectiveness, which are of clear importance to both patients and healthcare systems [73].

This study has several limitations. Substantial heterogeneity in trial design and reporting reduces the precision of subgroup inferences. Many included trials were small, and some had an unclear or high risk of bias in allocation concealment or blinding, which may have influenced effect estimates [74]. The absence of standardized imaging protocols and inconsis-

tent reporting of concomitant therapies such as analgesics or antispasmodics further limit the ability to draw causal conclusions [75]. Although sensitivity analyses support the robustness of the primary findings, the possibility of residual confounding and selective reporting cannot be excluded [76].

This meta-analysis demonstrates that tamsulosin is effective and safe for promoting stone expulsion in patients with ureteral calculi. Compared with placebo, it significantly increases expulsion rates and reduces time to clearance without increasing adverse events. Nevertheless, the substantial heterogeneity among studies highlights the need for large, well-designed randomized controlled trials to refine patient selection and to further assess long-term outcomes, cost-effectiveness, and quality of life associated with tamsulosin-based medical expulsive therapy.

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Disclosure of conflict of interest

None.

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Table S1. Sensitivity analysis of meta-analysis between stone expulsion rate and follow-up time

	RR	95% CI
All trials	1.40	1.27, 1.53
Using a fixed-effect model	1.22	1.18, 1.25
Excluding trials with Autorino 2005	1.40	1.27, 1.54
Excluding trials with Bak 2007	1.40	1.27, 1.54
Excluding trials with Cervenàkov 2002	1.41	1.28, 1.55
Excluding trials with De 2006	1.42	1.29, 1.57
Excluding trials with Dong 2009	1.41	1.28, 1.54
Excluding trials with Ferre 2009	1.41	1.28, 1.55
Excluding trials with Küpeli 2004	1.40	1.27, 1.53
Excluding trials with Li 2020	1.40	1.28, 1.54
Excluding trials with Porpiglia 2006	1.40	1.27, 1.53.
Excluding trials with Wang 2008	1.40	1.27, 1.54
Excluding trials with Zhou 2011	1.42	1.29, 1.56
Excluding trials with Abdel-Meguid 2010	1.40	1.27, 1.54
Excluding trials with Agrawal 2009	1.38	1.26, 1.52
Excluding trials with Al-Ansari 2010	1.41	1.28, 1.55
Excluding trials with Aldemir 2011	1.39	1.27, 1.52
Excluding trials with Arrabal-Martin 2010	1.40	1.27, 1.54
Excluding trials with Balci 2014	1.36	1.25, 1.48
Excluding trials with Dellabella 2003	1.40	1.27, 1.54
Excluding trials with Dellabella 2005	1.42	1.29, 1.57
Excluding trials with El-Gamal 2012	1.38	1.26, 1.51
Excluding trials with Erturhan 2007	1.39	1.27, 1.53
Excluding trials with Griwan 2010	1.41	1.28, 1.55
Excluding trials with Han 2006	1.40	1.27, 1.54
Excluding trials with Hermanns 2009	1.42	1.29, 1.57
Excluding trials with Kaneko 2010	1.40	1.27, 1.54
Excluding trials with Kim 2007	1.38	1.26, 1.51
Excluding trials with Kirac 2013	1.41,	1.28, 1.55
Excluding trials with Lee 2014	1.40	1.27, 1.53
Excluding trials with Lojanapiwat 2008	1.39	1.27, 1.53
Excluding trials with Mauro 2024	1.43	1.31, 1.57
Excluding trials with Ochoa-Gomez 2011	1.42	1.29,1.56
Excluding trials with Sayed 2008	1.39	1.27, 1.53
Excluding trials with Turgut 2021	1.39	1.27, 1.53
Excluding trials with Ye 2017	1.44	0.97, 2.13
Excluding trials with Yencilek 2010	1.41	1.28, 1.54
Excluding trials with Yilmaz 2005	1.40	1.27, 1.54
Excluding trials with Maitra 2012	1.38	1.26, 1.51
Excluding trials with Resim 2005	1.41	1.28, 1.55
Excluding trials with Vincendeau 2010	1.42	1.29, 1.56

Table S2. Sensitivity analysis of meta-analysis between stone size and adverse drug reactions

	RR	95% CI
All trials	0.91	0.54, 1.51
Using a fixed-effect model	0.94	0.76, 1.16
Excluding trials with Agrawal 2009	0.76	0.46, 1.25
Excluding trials with Balci 2014	0.90	0.53, 1.55
Excluding trials with De 2006	0.89	0.52, 1.52
Excluding trials with Erturhan 2007	0.93	0.55, 1.58
Excluding trials with Hermanns 2009	0.85	0.50, 1.43
Excluding trials with Meltzer 2018	0.88	0.48, 1.60
Excluding trials with Resim 2005	0.91	0.54, 1.51
Excluding trials with Ye 2017	0.89	0.47, 1.72
Excluding trials with Arrabal-Martin 2010	0.93	0.55, 1.57
Excluding trials with Dellabella 2005	0.95	0.57, 1.59
Excluding trials with Küpeli 2004	0.88	0.52, 1.49
Excluding trials with Li 2020	1.07	0.66, 1.72
Excluding trials with Porpiglia 2006	0.88	0.52, 1.48
Excluding trials with Turgut 2021	1.06	0.64, 1.74
Excluding trials with Wang 2008	0.91	0.53, 1.54