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Effect of Tamsulosin on Stone Passage for Ureteral Stones: A Systematic Review and Meta-analysis

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Study objective: Tamsulosin is recommended for patients receiving a diagnosis of a ureteral stone less than 10 mm who do not require immediate urologic intervention. Because of conflicting results from recent meta-analyses and large randomized controlled trials, the efficacy of tamsulosin is unclear. We perform a systematic review and meta-analysis to investigate the effect of tamsulosin on stone passage in patients receiving a diagnosis of ureteral stone.

Methods: MEDLINE, EMBASE, and CENTRAL databases were searched without language restriction through November 2015 for studies assessing the efficacy of tamsulosin and using a double-blind, randomized, controlled trial design. Meta-analysis was conducted with a random-effects model and subgroup analyses were conducted to determine sources of heterogeneity.

Results: Eight randomized controlled trials (N=1,384) contained sufficient information for inclusion. The pooled risk of stone passage in the tamsulosin arm was 85% versus 66% in the placebo arm, but substantial heterogeneity existed across trials (I^2=80.2%; P<.001). After stratifying of studies by stone size, the meta-analysis of the large stone subgroup (5 to 10 mm; N=514) indicated a benefit of tamsulosin (risk difference=22%; 95% confidence interval 12% to 33%; number needed to treat=5). The meta-analysis of the small stone subgroup (<4 to 5 mm; N=533) indicated no benefit (risk difference=−0.3%; 95% confidence interval −4% to 3%). Neither meta-analysis for the occurrence of dizziness or hypotension showed a significant effect.

Conclusion: Tamsulosin significantly improves stone passage in patients with larger stones, whereas the effect of tamsulosin is diminished in those with smaller stones, who are likely to pass their stone regardless of treatment. [Ann Emerg Med. 2016;■:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Patients receiving a diagnosis of ureteral stones less than 10 mm who do not require immediate urologic intervention are observed for stone passage.[1,2] Medical expulsive therapy, including α-blockers, steroids, and calcium channel blockers, has been extensively studied as an adjunct to observation, potentially benefiting patients by facilitating stone passage and decreasing the need for urologic intervention. In accordance with the results of numerous randomized controlled trials and meta-analyses,[3-5] the American Urologic Association and European Association of Urology have recommended that patients with ureteral stones less than 10 mm be followed for stone passage and receive an appropriate medical therapy.[1,6] A recent Cochrane review of α-blockers, including 32 randomized trials of 5,684 participants, reported a significant improvement in stone passage.[7] However, the majority of trials included in this study were not placebo controlled and blinded and were considered at moderate to high risk of bias; only 7 of 32 trials were doubled blinded. Two subsequent multicenter randomized placebo-controlled trials did not show a significant benefit of tamsulosin, except in the most recent randomized trial, which suggested a benefit in a subgroup with larger stones (5 to 10 mm).[8,9] These conflicting results have led to considerable uncertainty in regard to the efficacy of tamsulosin for increasing the passage of ureteral stones.

The efficacy of tamsulosin is important to elucidate.[7] Urolithiasis is a common disorder because 1 in 11 persons in the United States experiences stone disease in his or her lifetime.[10] It is estimated there are now more than 2 million annual outpatient visits for urolithiasis in the United States.[11] Although urologists have been proponents

Editor's Capsule Summary

What is already known on this topic

There is contradictory evidence about the value of tamsulosin for ureteral stones.

What question this study addressed

Do differences in stone size explain conflicting trial results?

What this study adds to our knowledge

This meta-analysis of 8 trials and 1,384 patients found no improvement in stone passage from tamsulosin in the subset with smaller stones (<5 mm) but benefit in those with larger stones (number needed to treat 5).

How this is relevant to clinical practice

Tamsulosin is beneficial for larger (5 to 10 mm) ureteral stones only.

of α-blocker use, other clinicians who manage urolithiasis have used α-blockers at low rates.[11,12] A clear understanding of the value of tamsulosin would help clinicians to decide whether to offer this therapy to patients with a common, recurrent, painful, and costly problem. We chose to focus on tamsulosin because it is the most frequently studied α-blocker, recommended in urology treatment guidelines, and, in our experience, the most common medical expulsive therapy used by emergency physicians.[6,7]

Goals of This Investigation

We conducted a systematic review and meta-analysis to determine the effect of tamsulosin on stone passage in adults receiving a diagnosis of ureteral stones. We sought to overcome the limitations of previous meta-analyses by including only randomized, double-blind, placebo-controlled trials. We also conducted a subgroup analysis (stone size <5 versus 5 to 10 mm) to determine whether stone size modifies the effect of tamsulosin, as suggested by the latest trial.[9] This study will clarify the role of tamsulosin in patients receiving a diagnosis of ureteral stones less than 10 mm that do not require urgent intervention.

MATERIALS AND METHODS

The protocol for this systematic review and meta-analysis is available on the Prospero Web site (http://www.crd.york.ac.uk/PROSPERO/). Our study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for systematic reviews.[13] With the assistance of a medical librarian (E.W.), a search of MEDLINE, EMBASE, and CENTRAL databases to include citations from January 1966 to November 2015, limited to human subjects and without a language restriction, was undertaken. Abstracts were included in the search. Details of the search strategy are shown in Figure E1, available online at http://www.annemergmed.com. We reviewed bibliographies of identified studies and review articles and consulted with topic experts to identify additional studies not retrieved by the electronic search.

Two reviewers (R.C.W. and J.F.) independently screened titles and abstracts of all articles identified by the search. Disagreements between the reviewers concerning the decision to include or exclude a study were resolved by consensus and, if necessary, consultation with a third author (M.L.S.). The following eligibility criteria were used to select articles for this systematic review and meta-analysis: randomized, placebo-controlled, double-blind trials that assessed the effect of tamsulosin on stone passage among adult patients with radiographically confirmed ureteral stones of 10 mm or less. Studies were excluded if they did not provide a description of randomization, use of a placebo, or blinding; if tamsulosin was not compared with placebo; if stone passage was not measured; and if they examined posturologic interventions for stones (such as lithotripsy or ureteral stent placement). Studies were also excluded from the meta-analysis if correspondence with authors failed to provide data that would be amenable to pooling. The full texts of potentially relevant studies were then reviewed for articles meeting inclusion criteria. A final roster of included studies was identified through reviewer consensus. The 2 reviewers then independently abstracted data from the included studies. The agreement between reviewers for study inclusion was assessed with Cohen's κ.

Two investigators (R.C.W. and J.F.) independently abstracted data from the included articles. The Cochrane Group collection form for interventional reviews was used for data abstraction. The information extracted included trial name, year of publication, number and country of centers, recruitment period, number of patients in each treatment group, details about trial design (randomization, blinding, and allocation concealment), eligibility criteria, intervention, control therapy, baseline patient demographics, efficacy outcomes (stone passage), length of follow-up, safety outcomes (dizziness and postural hypotension), and outcomes among relevant subgroups of patients (small versus large stone size).

Two investigators (R.C.W. and J.F.) independently performed quality assessment. We used the Cochrane Collaboration's tool to assess the risk of selection,

performance, detection, attrition, and reporting biases among the included randomized trials.[14] In instances in which data were not readily available or clear in the studies, we contacted corresponding authors to gain clarification. If studies were found to be at high risk of bias, meta-analyses stratified by study quality could be performed.

Data Collection and Processing and Primary Data Analysis

Pooled risk differences with corresponding 95% confidence intervals (CIs) for each outcome of interest were calculated. The main outcome was the risk difference in stone passage after at least 3 weeks of observation. The risk of stone passage was defined as the ratio of the frequency of patients who were found to be stone free on follow-up to the total group of subjects in each study arm. Participants were considered to be stone free if they had a ureteral stone at baseline and no stone on follow-up computed tomography (CT) or kidney, ureter, and bladder radiographs. The secondary outcome was the risk difference in the 2 main adverse effects: self-reported dizziness and postural hypotension. The number needed to treat was calculated as the inverse of the risk difference in stone passage.

We conducted a subgroup analysis based on previous evidence suggesting that stone size (measured at the initial visit) is an important determinant of stone passage.[6,9,15] Furthermore, a recently published trial suggested that patients with large stones (5 to 10 mm) benefited from tamsulosin, whereas those with smaller stones (<5mm) did not.[9] We hypothesized that stone size modified the effect of tamsulosin and accounted for between-study heterogeneity, or could help resolve discrepancies between "negative-result" multicenter trials and previous meta-analyses.[16] Thus, we sought to conduct a prespecified analysis comparing the effect of tamsulosin in a small-stone (<5 mm) versus large-stone (5 to 10 mm) subgroup. We used the same outcome definitions of stone passage and time to stone passage for these subgroup analyses. Time to stone passage was not reported because this outcome is subjective and was not measured precisely or uniformly in the included studies.

Publication bias was explored with the use of funnel plots, the Egger regression asymmetry test, and the Beggs adjusted rank correlation test. For all meta-analyses, outcomes were pooled with the DerSimonian and Laird random-effects model, with weights calculated by the inverse variance method to control for heterogeneity. Heterogeneity in the summary statistics were assessed by the χ^2 test statistic and expressed as the I^2 statistic. Individual study authors were contacted for updated or individual patient data, but none were made available. All analyses were performed with Stata (version 13; StataCorp, College Station, TX).

RESULTS

Using the search terms, the search strategy yielded 991 references with potential relevance (Figure 1). After removal of duplicate records, 732 references underwent review of title and abstract, yielding 19 potentially relevant references, which were reviewed in full. Five studies were duplicates, 5 did not contain sufficient data to analyze in a meta-analysis, and 1 reported 1-week outcomes (versus 3- to 4-week outcomes). Authors for 7 studies were contacted for additional information,[8,17-22] and complete data were available in only 8 cases. Agreement between study abstractors was excellent (Cohen's κ=0.94 [95% CI 0.82 to 1.0]). The 8 studies included in the systematic review are shown in Table 1, comprising 1,384 participants. Included trials and patient characteristics are also displayed. Among the 8 placebo-controlled, double-blinded, randomized trials of tamsulosin in patients with ureteral stones, only 1 included ureteral stones of all locations,[8] whereas the remaining studies included distal ureteral stones identified by CT or kidney, ureter, and bladder radiographs. Four studies were conducted in an emergency department (ED) setting,[8,9,19,23] and 4 were conducted in urology clinics in a number of different countries,[17,18,21,24] including Australia, Egypt, France, India, Qatar, Switzerland, the United Kingdom, and the United States.

Tamsulosin 0.4-mg pills were used as the intervention in all trials. Six trials provided tamsulosin for 28 days, 1 provided the drug for 21 days,[21] and the remaining study provided tamsulosin for 42 days.[23] The control group in each study received a placebo pill.

The main outcome of all included studies was stone passage, also referred to as "stone clearance" or "stone-free rate." In 7 of the 8 studies, this outcome was defined as the absence of a ureteral stone on imaging, either CT or kidney, ureter, and bladder radiographs, at the end of the study period (after a stone was visualized on baseline imaging). In 1 study, stone passage was defined as the absence of urologic intervention.[8] We used results from 28 days whenever possible to avoid heterogeneity.

The risk of bias for each study is described in Table E1, available online at http://www.annemergmed.com. All of the 8 studies were found to be at low risk of bias; 1 study was initially found to be at moderate risk of bias because of lack of description of blinding and allocation concealment in the published article.[18] However, we chose to include this study because contact with the

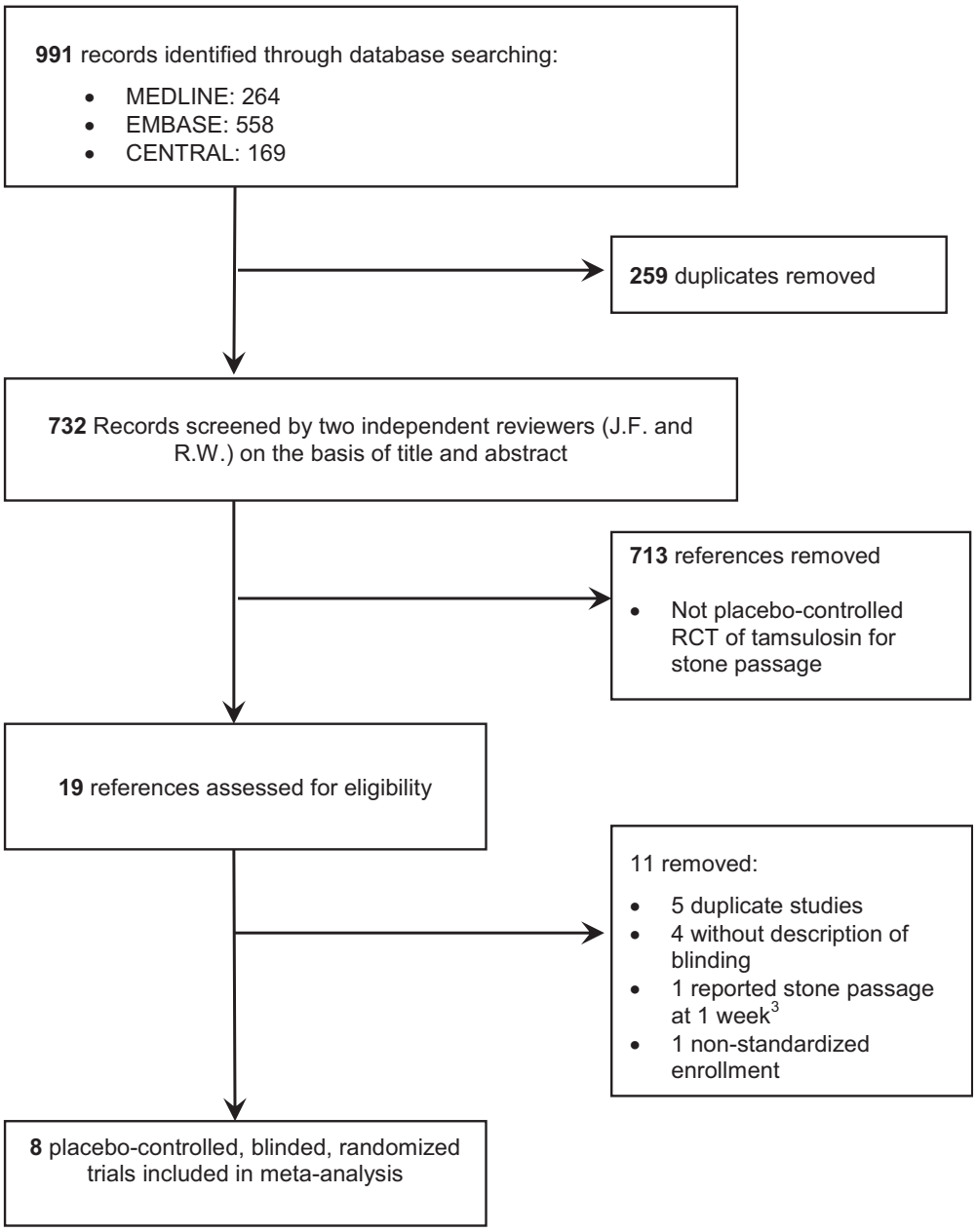

Figure 1. Outline of study selection and inclusion.

author confirmed that the study was, in fact, placebo controlled and double blinded. Four of the 8 studies were found to have an unclear risk of attrition bias because participants who were lost to follow-up were excluded from the final analyses.

The percentage of participants who experienced stone passage for tamsulosin and placebo cohorts is shown in Table 2. The pooled risk of stone passage in the tamsulosin arm was 85%; in the placebo arm, 66%. In the primary meta-analysis including 8 studies, tamsulosin resulted in increased stone passage (risk difference=17%; 95% CI 6% to 27%). However, the I^2 statistic was 80.2% ($P<.001$), indicating substantial heterogeneity. A forest plot of all studies sorted by stone size can be found in Figure E2 (available online at http://www.annemergmed.com), suggesting that this heterogeneity can in part be explained by differences in stone size.

In a preplanned subgroup analysis, the pooled estimate for stone passage in the subgroup of patients with large stones (minimum stone size of 4 mm) was calculated. Six of the 8 studies reported outcomes for a larger stone subgroup; however, the definition of stone size varied from

Table 1. Characteristics of included studies by publication date.

Study, Year	Setting	Participants	Intervention	Outcome Definition	Sample, N=1,384
Hermanns, 2009	Single urology clinic, Switzerland	Distal ureteral stone ≤7 mm	Tamsulosin 0.4 mg×21 days	Follow-up CT at 3 wk	90
Agrawal, 2009	Single urology clinic, India	Distal ureteral stone <10 mm	Tamsulosin 0.4 mg×28 days	Follow-up KUB at 4 wk	68
Abdel-Meguid, 2010	Single urology clinic, Saudi Arabia	Distal ureteral stone 4–10 mm	Tamsulosin 0.4 mg×28 days	Follow-up CT at 4 wk	150
Al-Ansari, 2010	Single ED, Qatar	Distal ureteral stone <10 mm	Tamsulosin 0.4 mg×28 days	Follow-up KUB at 4 wk	96
Vincendeau, 2010	6 EDs, France	Distal ureteral stone 2–7 mm	Tamsulosin 0.4 mg×42 days	Patient report of passage+KUB/CT by 6 wk*	121
El-Gamal, 2012†	Single urology clinic, Egypt	Distal ureteral stone ≥5 mm	Tamsulosin 0.4 mg×28 days	Follow-up CT at 4 wk	48
Furyk, 2015	5 EDs, Australia	Distal ureteral stone ≤10 mm	Tamsulosin 0.4 mg×28 days	Follow-up CT at 4 wk	316
Pickard, 2015‡	24 "secondary care units," UK	Ureteral stone ≤10 mm*	Tamsulosin 0.4 mg×28 days	Absence of urologic intervention at 4 wk	495

KUB, Kidney, ureter, and bladder imaging.
*Outcome measures at 28 days available.
†The tamsulosin and placebo arms were included in this analysis.
‡The distal stone subgroup was included in this analysis.

study to study because some studies used a cutoff of 4 mm, whereas others used 5 mm. Two studies exclusively enrolled participants with a minimum stone size of 4 mm.[17,24] Large stone size definitions are listed in Figure 2. In the subgroup meta-analysis of large stone size, the I^2 statistic was 33.1% *(P*=.19), with an RD in stone passage of 22% (95% CI 12% to 33%), or a number needed to treat=5. In the subgroup meta-analysis of small stone size (maximum stone size 5kmm), the I^2 statistic was 0% (*P*=.43), with an RD in stone passage of –0.03% (95% CI –3.9% to 3.3%), suggesting no benefit from tamsulosin on stone passage in patients with smaller stones. However, this subgroup meta-analysis is limited to only 4 studies in which data for small stones were available.

The percentage of participants who experienced dizziness for the tamsulosin and placebo cohorts is shown in Table 3. The pooled analysis included 8 studies with an $I^{2=}$=67.8% (*P*=.003), and the RD for the occurrence of dizziness=0.2% (95% CI –2.1% to 2.5%).

For orthostatic hypotension, the pooled analysis included 8 studies with an I^2 statistic=0% (*P*=.54), and the RD for postural hypotension=0.1% (95% CI –0.4% to 0.5%). Neither analysis identified a significant difference in either harm-related outcome between the tamsulosin and placebo cohorts.

Visual inspection of the funnel plot did demonstrate asymmetry (Table E2, available online at http://www.annemergmed.com), and there was evidence for

Table 2. Effect of tamsulosin in distal ureteral stones less than 10 mm on stone passage in order of stone size.

Study	Year	Size, mm	Tamsulosin, N=698, No. (%)	Placebo, N=686, No. (%)	Risk Difference, % (95% CI)	Relative Risk (95% CI)
Vincendeau	2010	3.1	43/60 (71.7)	39/61 (63.9)	7.7 (–8.7 to 24.3)	1.12 (0.88 to 1.43)
Furyk	2015	3.7*	140/161 (87.0)	127/155 (81.9)	5.0 (–3.0 to 13.0)	1.06 (0.97 to 1.17)
Hermanns	2009	3.9*	39/45 (86.7)	40/45 (88.9)	–2.2 (–15.7 to 11.3)	0.98 (0.84 to 1.14)
Pickard	2015	4.6	216/249 (86.7)	202/246 (82.1)	4.6 (–1.7 to 11.0)	1.06 (0.98 to 1.14)
Abdel-Meguid	2010	5.5*	61/75 (81.3)	42/75 (56.0)	25.3 (11.1 to 39.6)	1.45 (1.16 to 1.82)
Al-Ansari	2010	6.0	41/50 (82.0)	28/46 (60.9)	21.1 (3.5 to 38.8)	1.35 (1.03 to 1.76)
Agrawal	2009	6.3	28/34 (82.3)	12/34 (35.3)	47.1 (26.5 to 67.6)	2.33 (1.44 to 3.77)
El-Gamal†	2012	6.4	21/24 (87.5)	10/24 (41.7)	45.8 (22.1 to 69.6)	2.1 (1.28 to 3.45)
Pooled, %			85	66	16.7 (6.4 to 26.9) I^2=80.2% *P*<.001	1.22 (1.07 to 1.40) I^2=78.3% *P*<.001

*Authors provided median stone size; no asterisk indicates authors provided mean stone size.
†El-Gamal: data restricted to the 5- to 8-mm-stone subgroup in the study; the 8- to 11-mm subgroup was excluded because it included individuals with stones larger than 10 mm.

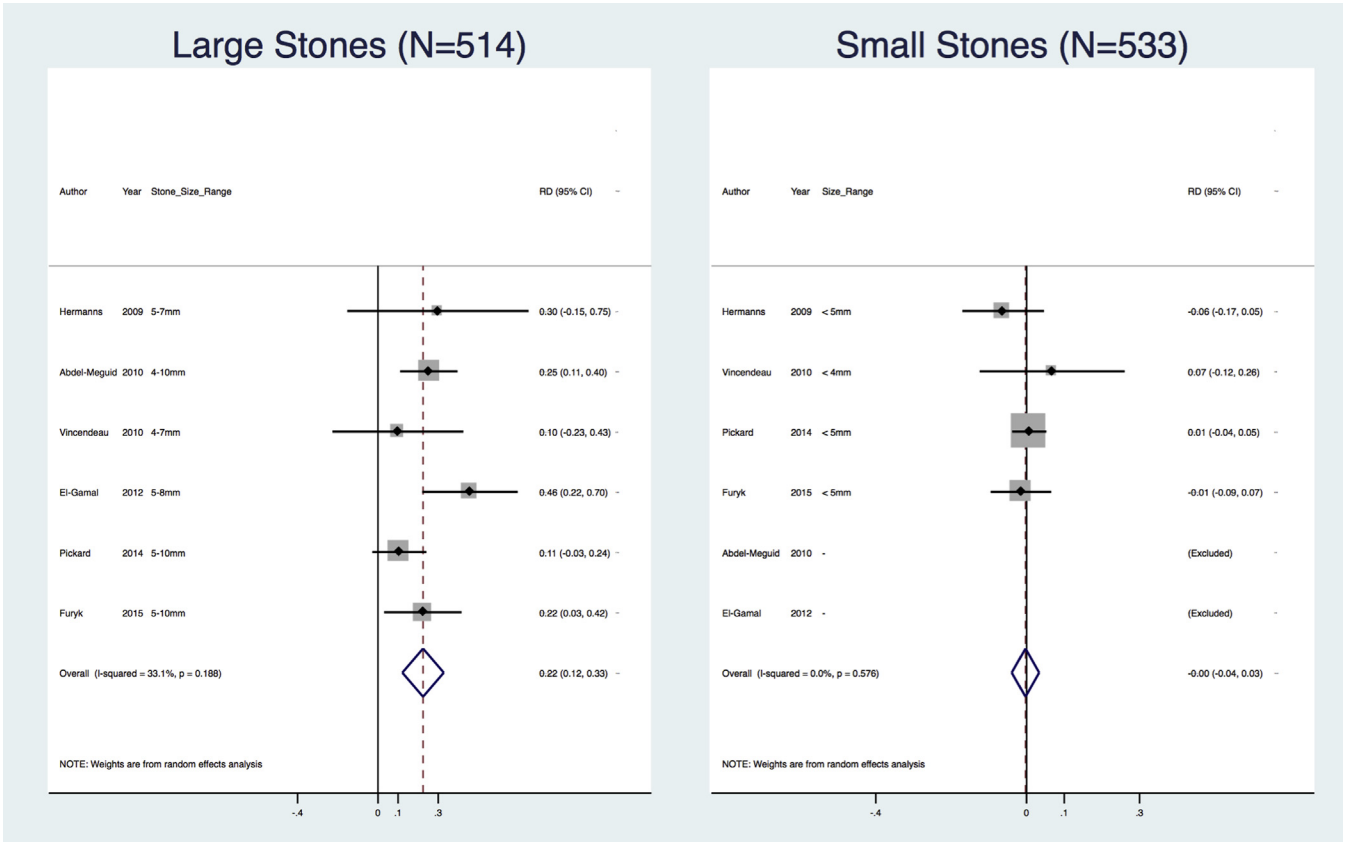

Figure 2. Forest plot: effect of tamsulosin in large versus small distal ureteral stones.

publication bias when data were analyzed by Egger's test (P=.02), but not the Beggs test.

LIMITATIONS

We chose to include randomized, placebo-controlled, blinded trials of tamsulosin. In accordance with visual inspection of the funnel plot (Figure E3, available online at http://www.annemergmed.com), as well as Egger's test, we found evidence to suggest publication bias. It is possible that negative-result small studies were not published. To minimize this bias, abstracts were searched, and several authors were contacted. Ultimately, we did not uncover any unpublished reports of high enough quality to permit inclusion in this meta-analysis.

All of the studies enrolled subjects according to the presence of a ureteral stone on CT or kidney, ureter, and bladder radiographs. This eligibility criterion differs from that of current practice because not all patients receiving a

Table 3. Incidence of dizziness and postural hypotension, tamsulosin versus placebo.

			Dizziness			Postural Hypotension		
Study	**Year**	**N**	**Tamsulosin**	**Placebo**	**RD (95% CI)**	**Tamsulosin**	**Placebo**	**RD (95% CI)**
Vincendeau	2010	126	0/64	0/62	0 (−3.1 to 3.1)	6/64 (9.2)	3/62 (4.8)	4.5 (−4.4 to 13.5)
Furyk	2015	316	46/169 (27.2)	36/173 (20.8)	6.4 (−2.6 to 15.4)	3/169 (1.8)	2/173 (1.2)	0.6 (−1.9 to 3.2)
Hermanns	2009	90	0/45	1/45 (2.2)	−2.2 (−8.2 to 3.7)	0/45	0/45	0 (−4.2 to 4.2)
Pickard	2015	757	0/378	1/379 (0.3)	−0.3 (−1.0 to 0.5)	0/378	0/379 (0.3)	0 (−0.5 to 0.5)
Abdel-Meguid	2010	150	0/75	0/75	0 (−2.6 to 2.6)	0/75	0/75	0 (−2.6 to 2.6)
Al-Ansari	2010	96	2/50 (6.0)	2/46 (4.4)	−0.3 (−8.4 to 7.7)	1/50 (6.0)	0/46 (4.4)	2.0 (−3.5 to 7.5)
Agrawal	2009	68	4/34 (11.8)	2/34 (5.9)	5.9 (−7.5 to 19.3)	0/34 (11.8)	0/34 (5.9)	0 (−5.6 to 5.6)
El-Gamal	2012	94	0/48	0/46	0 (−4.1 to 4.1)	0/48	0/46	0 (−4.1 to 4.1)
Pooled, %					0.2 (−2.1 to 2.5)			0.1 (−0.4 to 0.5)
					I^2=67.8%			I^2=0%
					P=.003			P=.54

N, Study sample size.

diagnosis of urolithiasis undergo CT or kidney, ureter, and bladder imaging.[11] Seven of 8 studies enrolled only patients with distal ureteral stones, and the remaining study included ureteral stones located in the proximal or midureter.[8] Thus, we were unable to conduct a meta-analysis of nondistal studies. The majority of stones are thought to be found in the distal ureter because distal stones composed 65% of all ureteral stones in the aforementioned large multicenter trial.[8] Proximal stones may continue to descend and become distal stones, and as such, there may be an ultimate benefit to tamsulosin during a longer period of observation. Similarly, all studies excluded stones measuring more than 10 mm. Experts recommend urologic intervention in these patients; however, it is possible that passage of even these very large stones can be facilitated by tamsulosin. Management of these patients should include consultation with a urologist.

Previous reviews of randomized trials have shown inconsistencies in the reporting of harms-related outcomes.[25,26] There is substantial heterogeneity in the reported incidence of dizziness, with some studies reporting 20% of both cohorts experiencing dizziness and several other studies reporting no harm-related events.[17,18,24,27] Also, no included studies calculated the power to detect differences in adverse effects. These limitations should be taken into account when the reliability of the dizziness and postural hypotension findings is considered, even when combined in a meta-analysis.

Substantial heterogeneity was identified in our main analysis, calling into question the reliability of a single pooled estimate with all studies. This heterogeneity likely stemmed from variation in clinical settings (ED versus outpatient urology office), study populations, inclusion criteria, follow-up assessment, and outcome measurements. We sought to control for heterogeneity between studies by using a random-effects model and also conducted a subgroup analysis based on stone size, which explains a portion of the heterogeneity that was encountered.

DISCUSSION

In a systematic review and meta-analysis of 8 randomized, double-blind, placebo-controlled trials, we found that tamsulosin improves stone passage in a subgroup of participants with large distal ureteral stones. In patients with a confirmed distal ureteral stone from 5 to 10 mm, a trial of tamsulosin 0.4 mg once daily for 28 days or until stone passage is likely to improve stone passage. In these patients, the number needed to treat for tamsulosin to induce 1 patient to pass a stone who otherwise would not have may be as low as 3 or as high as 8. The subgroup analysis of participants with smaller stones was limited to 4 studies, which did not suggest a significant effect. This diminished effect in patients with smaller stones may be explained by the overall high likelihood of stone passage because more than 80% of those with a stone less than 5 mm experienced spontaneous stone passage in the placebo arm.

The results of our meta-analysis suggest an explanation for the discrepancies between previous meta-analyses and the recent large multicenter pragmatic trial by Pickard et al.[8] The authors of this randomized, double-blind, placebo-controlled, pragmatic, multicenter trial reported a lack of benefit of tamsulosin for patients with ureteral stones up to 10 mm. The discrepancies between this well-conducted trial and our meta-analysis are likely due to differing inclusion criteria and stone sizes. Pickard et al[8] included participants with ureteral stones of all locations (proximal, midureter, and distal), whereas the 7 remaining trials in this meta-analysis included only those with distal stones. Thus, we chose to include the authors' distal ureteral stone subgroup, which appeared to show a weak trend toward a benefit in the tamsulosin arm (RD=5%; 95% CI –2% to 11%). We believe that the subgroup of participants with large, distal stones from the study by Pickard et al[8] would have shown a significant improvement in stone passage, but we were unable to obtain the additional data required. After ongoing correspondence and unsuccessful requests for data from Pickard, we ultimately elected to use the best available results in the published article for the purposes of pooling data. Thus, we used large stones of all locations in the large stone subgroup analysis.

We believe the subgroup analysis based on stone size identified in this meta-analysis is likely to be valid. This subgroup analysis is suggested by a previous study, in which tamsulosin improved stone passage in large stones (5 to 10 mm), but not in smaller ones (<5 mm).[11] The role of stone size as a modifier of the effect of tamsulosin on stone passage is biologically plausible because stone size is a known predictor of stone passage. Small stones have a high rate of passage, whereas large ones are less likely to pass, and it seems logical that tamsulosin mainly benefits patients with more recalcitrant stones. The effect of stone size is consistent across the 4 studies that included both small and large subgroups because tamsulosin is associated with a benefit in the large stone subgroups and not in the small stone subgroup.[8,9,21,27] Chance alone is unlikely to explain the difference in the effect of tamsulosin because the 95% CIs of the effect on small versus large subgroups do not overlap.

We updated the Cochrane review of α-blockers, which included studies up to 2012. This review concluded that the use of tamsulosin in patients with ureteral stones results in a higher stone-free rate (relative risk 1.48; 95% CI 1.32 to 1.67) compared with standard therapy. In contrast to the

Cochrane review, our main finding suggests that tamsulosin is efficacious in patients with larger stones (relative risk 1.36; 95% CI 1.18 to 1.56) and not with smaller ones. This difference is likely due to our inclusion of blinded placebo-controlled trials, whereas the Cochrane review included 24 small, single-center trials, the majority of which (19/24) did not describe use of a placebo and blinding. Additionally, 2 recent multicenter studies not included in the Cochrane review were included in our updated meta-analysis.

Tamsulosin did not appear to increase the incidence of dizziness or orthostatic hypotension in the included studies. These results differ from those of the most recent previous meta-analysis, in which the adverse events were combined. Patients who received an α-blocker were 2.7 times more likely to experience a number of adverse events, such as dizziness, palpitations, headache, rhinitis, retrograde ejaculation, and fatigue.[7] In addition, a large observational study found a significant association between tamsulosin use and hypotension necessitating hospital admission in patients with a mean age of 62 years and with benign prostatic hypertrophy.[28] Our results differ, likely because of the restriction to the most serious adverse events, dizziness and orthostatic hypotension. In addition, we limited our analysis to tamsulosin in placebo-controlled, blinded studies with a low risk of bias. However, we would maintain caution when prescribing tamsulosin because the results of our meta-analysis were limited by substantial heterogeneity and likely underpowered. The main exclusion criteria in the randomized trials in regard to patient safety included hypotension; concurrent α-, calcium channel, or beta-blocker use; allergic reaction to α-blockers; and pregnancy.

In accordance with the findings of this study, we strongly recommend the use of tamsulosin in patients receiving a diagnosis of large distal ureteral stones (5 to 10 mm). Because of the different cutoffs used in the included trials (4 versus 5 mm), the effect of tamsulosin is less certain for patients with a 4-mm stone, but we believe that it could be offered after a discussion with the patient about the risks and benefits of treatment. For stones less than 4 mm, we believe it is reasonable to avoid prescribing a likely unnecessary medication but acknowledge that in some circumstances (such as for patients who have previously needed surgical intervention for small stones) clinicians may choose to test a course of tamsulosin. Either course would be reasonable initially because the benefit of tamsulosin in this group of patients is likely to be modest, if any, but the harms from the drug appear to be minimal.

This meta-analysis also provides evidence for clinicians to discuss the likelihood of stone passage with their patients because those receiving a diagnosis of ureteral stones are often interested in knowing what to expect in regard to stone passage after an initial ED visit. A previous meta-analysis of 224 participants found that 68% of ureteral stones less than or equal to 5 mm passed spontaneously and 47% of those greater than 5 mm would pass spontaneously.[1] In our meta-analysis, we found that the overall stone passage rate at 28 days for distal ureteral stones in the placebo arm (694 participants) was 64%, with an 86% rate of stone passage in smaller stones (less than 4 to 5 mm) and 57% rate in patients with larger stones. It is unclear why the rate of stone passage is higher in the control group from our review. We believe that the method of ascertaining the stone passage outcome in 7 of the 8 included studies—repeated imaging—is likely to be accurate. Similarly, if administered tamsulosin, patients can expect an 85% rate of stone passage for smaller stones and a 79% rate for larger stones.

In conclusion, there is strong evidence to suggest that tamsulosin improves stone passage in patients with large stones (5 to 10 mm), whereas the effect of tamsulosin is unclear for those with stones less than 4 mm, who are likely to pass their stone regardless of treatment.

Supervising editor: Steven M. Green, MD

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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

Figure E1. Search strategy in steps.

Table E1. Risk of bias in included studies.

Risk of bias domain	Hermanns, 2009	Agrawal, 2009	Abdel Meguid, 2010	Al-Ansari, 2010	Vincendeau, 2010	El-Gamal, 2012	Furyk, 2015	Pickard, 2015
Random-sequence generation (selection bias)	Low	Low	Low	Low	Low	Low	Low	Low
Allocation concealment (selection bias)	Low	Low*	Low	Low	Low	Low	Low	Low
Blinding of participants (performance bias)	Low	Low*	Low	Low	Low	Low	Low	Low
Blinding of outcome assessment (detection bias)	Low	Low	Low	Low	Low	Low	Low	Low
Incomplete outcome data (attrition bias)	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
Selective outcome reporting (reporting bias)	Low	Low	Low	Low	Low	Low	Low	Low
Summary assessment	Low	Low	Low	Low	Low	Low	Low	Low

*Authors confirm that this trial is a randomized, double-blinded, placebo-controlled trial.

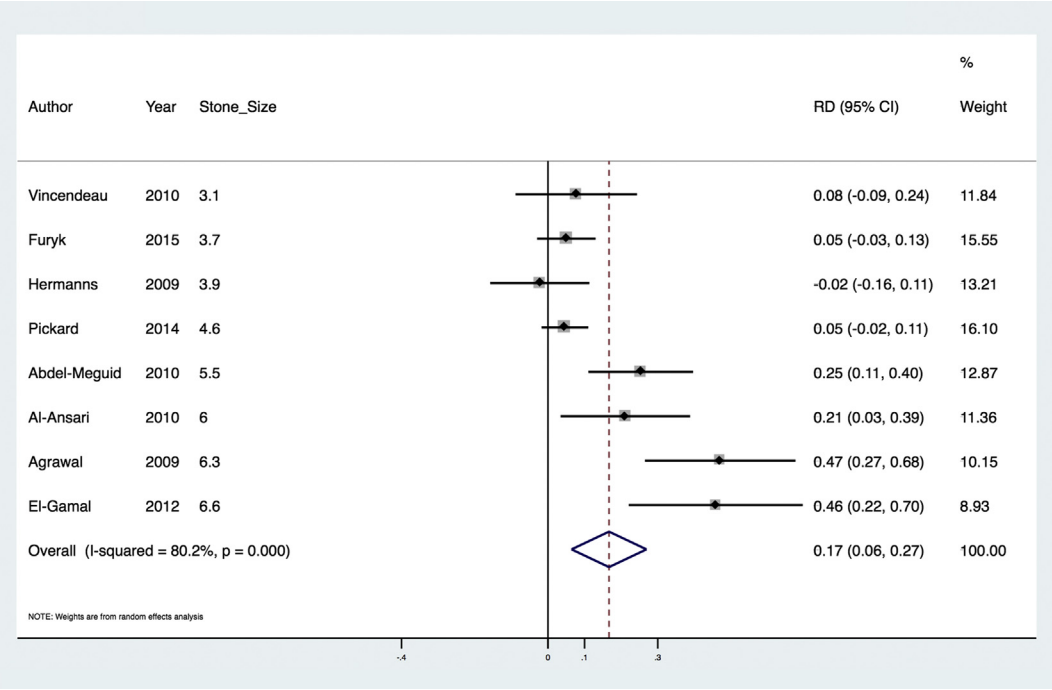

Figure E2. Forest plot: effect of tamsulosin in all studies by stone size.

Table E2. The effect of tamsulosin in distal ureteral stones on stone passage.

Study	Year	N	Size, mm	Tamsulosin	Placebo	Risk Difference, % (95% CI)
Subgroup analysis of larger stones (N=514)						
Vincendeau*	2010	33	4 to 7	11/16 (68.7)	10/17 (58.8)	9.9 (-22.7 to 42.5)
Abdel-Meguid	2010	150	4 to 10	61/75 (81.3)	42/75 (56)	25.3 (11.1 to 39.6)
Furyk	2015	77	5 to 10	30/36 (83.3)	25/41 (61.0)	22.4 (3.1 to 41.6)
Pickard†	2015	188	5 to 10	67/94 (71.3)	57/94 (60.6)	10.6 (-2.8 to 24.1)
El-Gamal	2012	48	5 to 8	21/24 (87.5)	10/24 (41.7)	45.8 (22.1 to 69.6)
Hermanns	2009	18	5 to 7	8/11 (72.7)	3/7 (42.9)	29.9 (-15.3 to 75.0)
Pooled, %				79	57	22.5 (12.1 to 32.8)
						I^2=33.1%
						P=.19
Subgroup analysis of smaller stones (N=533)						
Vincendeau*	2010	88	<4	32/44 (72.7)	29/44 (65.9)	6.8 (-12.4 to 26.0)
Furyk	2015	239	<5	110/125 (88.0)	102/114 (89.5)	-1.5 (-9.5 to 6.5)
Pickard†	2015	188	<5	149/155 (96.1)	145/152 (95.4)	0.7 (-3.8 to 5.2)
Hermanns	2009	18	<5	31/34 (91.2)	37/38 (97.4)	-6.2 (-17.0 to 4.6)
Pooled, %				85	86	-0.3 (-3.9 to 3.3)
						I^2=0%
						P=.58

*Stone passage at 28 days was used for this analysis.
†Pickard did not report distal stone outcomes stratified by stone size; these data represent results from patients with large stones at all locations in the ureter.

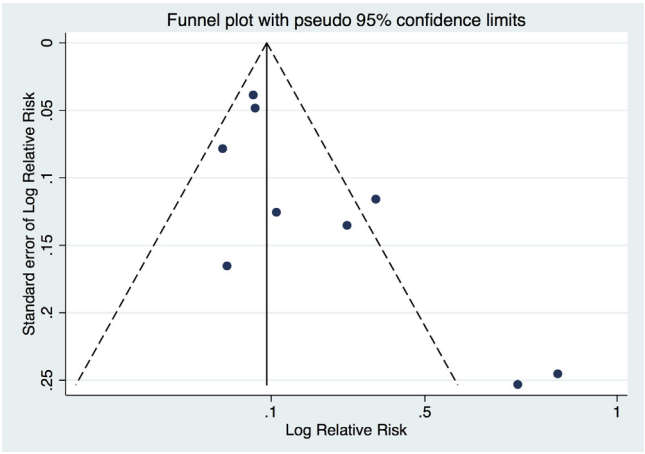

Figure E3. Funnel plot to diagnose publication bias.