Critical Review Form
Therapy

Furyk JS, Chu K, Banks C, Greenslade J, Keijzers G, Thom O, Torpie T, Dux C, Narula R. Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. Ann Emerg Med. 2016 Jan;67(1):86-95.e2.

Objectives: **"to assess the efficacy of tamsulosin 0.4 mg orally daily for 28 days compared with placebo in the management of patients with distal ureteric stones less than or equal to 10 mm in diameter and being discharged home from the ED with prespecified subgroups of stones less than 5 mm and 5 to 10 mm." (p. 87)**

Methods: **This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 5 hospitals in Queensland, Australia (4 tertiary and 1 regional district hospital). Patients older than 18 years in age with symptoms of a ureteric stone and a calculus 10 mm or less in diameter visualized in the distal ureter on CT were eligible for enrollment. Exclusion criteria included temperature greater than 38 degrees Celsius, estimated GFR < 60 mL/min, solitary kidney, transplanted kidney, history of ureteral stricture, known allergy to the study medication, current use of calcium channel blocker or alpha blocker, hypotension (systolic BP < 100 mm Hg), pregnancy, or planned pregnancy.**

Patients were randomized to placebo or tamsulosin 4 mg, to be taken daily for 28 days or until stone passage (defined by evidence of stone on urine straining). All patients were asked to record symptoms in a "patient diary" and were contacted for telephone follow-up at 7, 14, 21, and 28 days following enrollment. Information collected included number of pain episodes, worst pain score during a 24-hour period, and whether or not they were currently pain free, as well as any potential adverse events from study medication. At 28 days following enrollment, patients underwent a limited pelvic CT scan to definitively determine stone passage.

The two primary outcomes were stone expulsion (defined as absence of stone on CT at 28 days) and time to stone expulsion (defined as self-reported passage on urine straining or the first day of a 48-hour pain-free period, with no stone on 28-day CT). Secondary outcomes included ED return visits or hospital admission, total analgesia requirements, pain scores, need for urologic intervention, infection, renal impairment, days off work, and adverse effects.

A total of 403 individuals were enrolled, of whom 3 were excluded due to lack of stone on the initial CT (1 in the tamsulosin group and 2 in the placebo group) and 7 were excluded due to lack of a distal stone (3 in the tamsulosin group and 4 in the

placebo group). This left 393 patients in the final analysis: 198 in the tamsulosin group, 195 in the placebo group.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized "in permuted blocks of random lengths stratified by hospital and stone size ("small" and "large" stones being < 5 mm and 5 to 10 mm, respectively)." (pp. 87-88)
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Sequentially numbered study packs were securely stored at the study sites. The randomization study sequence was produced with a computer-generated program...by a clinical trial pharmacist not otherwise involved in the study, and was securely stored and known only to the trial pharmacist." (pp. 87-88)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. At 7 days, over 20% of patients in both groups already reported being less than fully compliant. This percent increased at each subsequent telephone follow-up. Despite this, patients were analyzed in the group to which they were randomized (intention to treat analysis).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, stone size and location, and renal function. They did not assess other medical comorbidities or history of prior stones.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "Investigators, the treating physician, and patients were blinded to the allocation for the duration of the study and data analysis." (p. 88)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of	No. Patients were blinded to group allocation,

	group allocation?	and were responsible for self-reporting pain scores, analgesia use, stone passage, and adverse effects. CT scans performed at 28 days to evaluated for stone passage were read by radiologists blinded to group allocation. Observer bias seems very unlikely in this study.
4.	Was follow-up complete?	No. Ten patients in the placebo group and 15 in the placebo group were completely lost to follow-up. Information on time to stone passage was available for 189 patients in the tamsulosin group and 188 in the placebo group. Only 161 patients (81.3%) in the tamsulosin group and 155 (79.5%) in the placebo group received a 28-day follow-up CT. Among patients with large stones, 77 had a 28-day CT (36 in the tamsulosin group and 41 in the placebo group). A total of 32 patients in each group (16%) had no data to assess either primary outcome.
II.	**What are the results ?**	
1.	How large was the treatment effect?	Stone passage by CT scan: • For all patients, stone passage occurred in 140 (87.0%) tamsulosin patients and 127 (81.9%) placebo patients, for an absolute risk reduction (ARR) of 5.1% (95% CI -3.0% to 13.0%). • Among patients with large stones, passage occurred in 30 patients (83.3%) in the tamsolusin group and 25 (61.0%) in the placebo group, for an ARR of 22.4% (95% CI 3.1% to 41.6%) and a NNT of 4.5. • Among patients with small stones, passage occurred in 110 patients (88.0%) in the tamsulosin group and 102 patients (89.5%) in the placebo group, for an ARR of -1.5% (95% CI -9.5% to 6.5%). Time to stone passage: • The median time to stone passage was not significantly different between the two groups: 7 days in the tamsulosin group (95% CI 5 to 10 days) and 11 days in the placebo group (95% CI 6 to 14 days), p = 0.10. Secondary outcomes: • The two groups did not differ with regards to repeat ED visits, hospital admission, or need

		for urologic intervention. • The two groups were similar with regards to number of oxycodone and indomethacin tabs taken, median number of pain episodes reported, and proportion of patients with a worst pain score greater than 0 at days 7, 14, 21, and 28. • There was no difference in the number of patients with a positive urine culture of renal impairment, or patients with adverse events.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. While the study was conducted in the Austraila, these were emergency department patients diagnosed with ureteral colic, and could be expected to be similar in most regards to patients with ureteral colic in the US. While all patients were diagnosed by CT, and at least some of our patients are diagnosed by ultrasound, it seems likely that the results would apply to both groups.
2.	Were all clinically important outcomes considered?	Mostly yes. They evaluated stone passage, pain, need for hospital admission or urologic intervention, infection, and adverse events from study medication. They did not assess quality of life or healthcare costs.
3.	Are the likely treatment benefits worth the potential harm and costs?	

Limitations:

1. **Outcome data for one of the primary outcomes (stone expulsion based on CT) was only available for around 80% of patients (attrition bias).**

2. **Compliance with study medication was generally poor in both groups. While this may reflect a real-world scenario, it does not necessarily speak to the efficacy of tamsulosin in this regard.**

3. **The conclusion that tamsulosin is effect for larger stones is based on a subgroup analysis. Even when pre-specified, such an analysis is generally considered to be hypothesis generating rather than practice changing.**

4. **The primary outcome, stone passage by CT scan at 28-days, is not necessarily a patient-centered outcome. The authors note that very few patients had ongoing pain by this time, and it may not be relevant if an asymptomatic stone is still present.**

Bottom Line:

This methodologically sound, blinded, randomized controlled trial found no benefit to giving tamsulosin to patients with distal ureteral stones with an ARR of 5.1% (95% CI -3.0% to 13.0%). A pre-specified subgroup analysis of patients with larger stones (5-10 mm) demonstrated an increase in the proportion of patients with stone expulsion at 28 days with tamsolusin compared to placebo. This result, while interesting, should be considered "hypothesis generating," and warrants further research.