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α-Blockers for uncomplicated ureteric stones: a clinical practice guideline

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Objective

To develop an evidence-based recommendation concerning the use of α-blockers for uncomplicated ureteric stones based on an up-to-date Cochrane review, as the role of medical expulsive therapy for uncomplicated ureteric stones remains controversial in the light of new contradictory trial evidence.

Methods

We applied the Rapid Recommendations approach to guideline development, which represents an innovative approach by an international collaborative network of clinicians, researchers, methodologists and patient representatives seeking to rapidly respond to new, potentially practice-changing evidence with recommendations developed according to standards for trustworthy guidelines.

Results

The panel suggests the use of α-blockers in addition to standard care over standard care alone in patients with uncomplicated ureteric stones (weak recommendation based on low-quality evidence). The panel judged that the net benefit of α-blockers was small and that there was considerable uncertainty about patients' values and preferences. This means that the panel expects that most patients would choose treatment with α-blockers but that a substantial proportion would not. This recommendation applies to both patients in whom the presence of ureteric stones is confirmed by imaging, as well as patients in whom the diagnosis is made based on clinical grounds only.

Conclusion

The Rapid Recommendations panel suggests the use of α-blockers for patients with ureteric stones. Shared decision-making is emphasised in making the final choice between the treatment options.

Keywords

α-blockers, ureteric stones, clinical practice guideline

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Introduction

This primary care Rapid Recommendation article is one of a series that provides GPs with trustworthy recommendations for potentially practice-changing evidence. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org/app#/guideline/1822), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences, and may want to use consultation decision aids in MAGICapp to facilitate shared decision-making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content for permission to reuse content in this article.

Definition of ureteric colic

Ureteric colic refers to acute pain episodes related to obstructing renal stones that have travelled into the ureter causing partial or complete obstruction. Spontaneous passage rates of small stones (≤4 mm) are reported to vary between 76% and 81% [1,2]. Larger stones may obstruct the ureter, cause episodic severe pain, and in rare cases have life-threatening complications such as sepsis.

Epidemiology

Urinary stones occur frequently worldwide. Prevalence rates of 7–13% are reported in North America, 5–9% in Europe, and 1–5% in Asia [3]. Rates vary greatly based on several factors such as: geography, climate, diet, fluid intake, genetics, gender, occupation, and age [3]. Incidence rates appear to have doubled over the last two decades, but are likely largely the result of increased utilisation of CT [4]. Estimated recurrence rates of urinary stones are between 35% and 50% within 5 years [5]. The 1-year incidence and prevalence of renal colic in general practice are estimated between two and 19 per 1000 patients in The Netherlands and Belgium [6,7].

Causes and risk factors

Most patients with ureteric stones form stones containing calcium, particularly calcium oxalate. Ureteric stones appear to be related to urine composition, which can be affected by patient lifestyle but also by certain conditions and diseases including: hypertension, gout, diabetes mellitus, obesity, and weight gain. Dietary risk factors for calcium oxalate stones that may play a role in the aetiology of stone disease include: a low dietary calcium intake, high oxalate intake (e.g. spinach, potato chips), high animal protein consumption, a low potassium intake, a high sodium intake, and a low fluid intake [8].

Symptoms

Flank pain that may radiate into the groin area, haematuria, as well as nausea and vomiting are classic symptoms of ureteric stones [6]. Less common symptoms include acute or vague abdominal pain, urinary urgency or frequency, difficulty urinating, and penile or testicular pain [8]. Some ureteric stones may be asymptomatic.

Diagnosis

The diagnosis of a suspected ureteric stone is based on clinical signs and symptoms, consisting of acute severe flank pain, the urge to move around, and haematuria [6]. The S.T.O.N.E. [stone size (S), tract length (T), obstruction (O), number of involved calyces (N), and essence or stone density (E)] risk assessment tool uses a combination of five criteria (sex, timing of onset of pain, origin, nausea, and haematuria) to stratify patients into a low, moderate or high probability of having a ureteric stone [9]. A urinary stone was confirmed in 73–99% of patients in the S.T.O.N.E. high-probability group (10–13 points) in a review of four subsequent validation studies in emergency settings [10]. Imaging practice varies in different part of the world. In some countries, management is based on clinical presentation only, whereas in others patients are imaged with CT, ultrasonography of the kidneys, ureter, and bladder or plain radiographs to confirm the diagnosis.

Treatment mechanism of α-blockers

α-Blockers reduce smooth muscle tone and are widely used to treat hypertension. Selective α_1-blockers (also called α-adrenergic blocking agents) constitute a subset of this drug class that preferentially block α_1-adrenergic receptors in the lower urinary tract. They are widely used to treat LUTS related to BPH [11]. α_1-Blockers as medical expulsive therapy (MET) for ureteric stones is an off-label indication of this drug.

Methodology

An international team, including patients with past experience of ureteric stones, GPs, emergency clinicians, urologists familiar with treating renal colic, epidemiologists, and methodologists constituted the guideline panel. No panel member had financial conflicts of interest; intellectual and professional conflicts of interests were minimised and described (Appendix S1). The panel met three times via web conference.

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach

The panel followed the *BMJ* Rapid Recommendations procedure for creating a trustworthy recommendation and used the GRADE approach to critically appraise the evidence

and create recommendations (Appendix S2) [12]. The GRADE approach provides guidance for rating quality of evidence and grading strength of recommendations in healthcare. It has important implications for those summarising evidence for systematic reviews, health technology assessment, and clinical practice guidelines. GRADE provides a systematic and transparent framework based on PICO (population, intervention, comparator and outcome)-structured questions with patient-relevant outcomes, a systematic summary of the evidence, and criteria for moving from evidence to recommendation or decision [13].

Importance of outcomes

The scope of the recommendations and the importance of potential relevant outcomes were individually rated by each panel member on a scale from 1 to 9 (7–9 critical, 4–6 important, 1–3 of limited importance). For each outcome, the mean scores were calculated and outcomes that scored ≥7 were selected for the recommendation, as recommended by GRADE [14]. Pain, hospitalisation, surgery, stone clearance, and major adverse events (MAEs) scored on average ≥7 and were thus rated as critical outcomes.

Summary of the evidence

The summary of the evidence was based on a linked Cochrane systematic review on the effects of α-blockers as MET for uncomplicated ureteric stones [15]. The latest literature search date of this review was November 2017, including unpublished data of a randomised clinical trial (RCT) of treatment with tamsulosin to promote passage of urinary stones by Meltzer et al. [16], and data from the single largest trial with >3000 patients from China [17].

From evidence to recommendations

The panel discussed the evidence and formulated specific recommendations. Formal methods were used to reach consensus (Appendix S2). For each outcome, the panel considered the balance of benefits, harms and burden of the interventions, the quality of evidence (Table 1), patient values and preferences, feasibility, and acceptability. The panel assessed the overall quality of evidence, the combined rating of the quality of evidence across all outcomes considered critical [18]. Recommendations can be strong or weak and for or against a certain course of action. The panel took the individual patient perspective when making these recommendations.

Results

Characteristics of studies

Table 2 provides an overview of the trial and patient characteristics of the systematic review. All studies were performed in emergency care settings. Exclusion criteria referred mainly to complicated stones or other abnormalities. There were 67 RCTs included, gathering data from 10 509 patients with confirmed ureteric stones. The intervention consisted of α-blockers (mostly tamsulosin), which were compared to either pain medication (52 studies) or to placebo (15 studies). Outcomes of the systematic review were stone clearance, stone expulsion time, number of pain episodes, dose of diclofenac, hospitalisations, and surgical interventions, as well as the occurrence of MAEs. The follow-up period in the studies included was mostly up to 4 weeks. Several predefined subgroup analyses were conducted based on stone size, stone location, and type of α-blocker [15]. A sensitivity analysis of solely high-quality trials focused on a subset of trials that had a low risk of bias. This sensitivity analysis formed the basis of the panel's recommendations for those outcomes where the quality of evidence was rated higher than it would be in the overall analysis. This was the case for one outcome (stone clearance; see paragraph 6.1 in the Cochrane review).

Benefits of α-blockers in patients with confirmed stones

α-Blockers in patients with confirmed ureteric stones increase stone clearance, probably decrease hospitalisations, and may slightly reduce the number of pain episodes. Stone clearance within the first 4 weeks was 764 per 1000 inpatients that received usual care compared to 833 per 1000 in those receiving α-blockers (high-quality evidence). The systematic review suggests that α-blockers are more effective for stones of ≥5 mm compared to smaller stones [15].

Approximately 141 per 1000 patients with usual care were hospitalised within 4 weeks, compared to 72 per 1000 in patients with α-blockers (moderate-quality evidence). Patients that received usual care experienced 2.2 pain episodes in 4 weeks compared to 1.5 in patients receiving α-blockers (low-quality evidence). There was little or no difference between usual care and α-blockers on surgical interventions. During the study period, 109 per 1000 patients that received usual care had surgery compared to 81 per 1000 in patients receiving α-blockers (low-quality evidence).

Harms of α-blockers in patients with confirmed stones

The systematic review evaluated the MAEs, defined as patients that experienced orthostatic hypotension, collapse, syncope, palpitations, or tachycardia [15]. There is little or no difference between usual care and α-blockers on MAEs in patients with confirmed stones. In all, 20 per 1000 patients in the usual care group had MAEs compared to

Table 1 Rating quality of evidence according to GRADE.

Grade	Definition
High quality	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality	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 quality	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Overall quality of evidence	The lowest quality of evidence for any of the critical outcomes determines the overall quality of evidence

25 per 1000 in groups that received α-blockers (low-quality evidence).

Benefits of α-blockers in patients with suspected stones

Whereas the body of evidence summarised in the Cochrane review that formed the basis of the recommendation was restricted to patients with a stones diagnosis confirmed by imaging, it is common practice in many parts of the world to treat patients based on clinical presentation alone. This adds uncertainty as to the magnitude of the benefit that these patients would experience. Even in a setting where the likelihood of an obstructing ureteric stone is high (for example, >80% based on the S.T.O.N.E. score), a subset of patients would not benefit as they do not have a ureteric stone. The panel judged that the benefits for patients with confirmed stones also apply to patients with suspected stones but that the actual effect size in this population is likely to be smaller as some patients with suspected stones will not have a stone. In addition, they expected substantial variation between how clinicians all over the world would treat patients with suspected stones, depending on the setting (primary or secondary care), the healthcare system, and on the experience of the clinician. For this reason, the panel downgraded the quality of evidence further. Therefore, in patients with suspected ureteric stones, the systematic review showed that α-blockers probably increase stone clearance (moderate quality), may decrease hospitalisation (low quality), and may slightly decrease the number of pain episodes (low quality). There is little or no difference between usual care and α-blockers on surgical interventions (low quality).

Harms of α-blockers in patients with suspected stones

Similarly, the panel judged that this evidence also applies to patients with suspected stones. Therefore, the panel judged that there may be little or no difference between usual care and α-blockers on the risk of MAEs (low-quality evidence).

Table 2 Characteristics of patients and studies included in the systematic review.

Data sources	67 studies	10 509 patients
Trial characteristics	Comparison:	52 studies
	• α-blockers vs standard therapy	15 studies
	• α-blockers vs placebo	
	Confirmation and follow-up examinations:	50 studies 4 studies
	• radiological examination	13 studies
	• no radiological examination (3 self-report, 1 'no intervention needed')	
	• unclear	
	Follow-up period: 1–8 weeks	41 studies
	• 4 weeks	
	Multicentre trial	10 studies
Patient characteristics	Number of patients enrolled, range	30–3450
	Mean age range, years	32–56
Type of α-blocker	Tamsulosin	54 studies
	Doxazosin	7 studies
	Alfuzosin	6 studies
	Silodosin	6 studies
	Naftopidil	3 studies
	Terazosin	2 studies

Patient values and preferences

The panel judged that patients might perceive small decreases in number of pain episodes as important because the pain intensity is very high. Small reductions in hospitalisations and avoiding surgery might also be relevant to patients. Patients may value the reduction in hospitalisations due to its major impact on one's life, inability to work, and the associated costs in some countries. Although stone clearance is considered of lesser importance, patients may feel reassured if a stone has passed. The panel judged that patient preferences may vary for these effects. The same considerations should apply to patients with confirmed and suspected ureteric stones.

Recommendation

The panel suggests the use of α-blockers in addition to standard care over standard care alone in patients with uncomplicated ureteric stones (weak recommendation based on low overall quality of evidence). The panel judged that the net benefit of α-blockers was small and that there was considerable uncertainty about patients' values and preferences. This means that the panel expects that most patients would choose treatment with α-blockers but that a substantial proportion would not. In both patients with confirmed and suspected ureteric stones, patients should be treated for 4 weeks or until the stone has passed. This

recommendation is intended for patients treated by GPs, urologists and emergency physicians.

The infographic (Fig. 1) provides an overview of the recommendations and the absolute benefits and harms of α-blockers for patients with confirmed and suspected ureteric stones. Detailed information can also be viewed through MAGICapp, including decision aids designed to support shared decision-making with patients (https://www.magicapp.org/app#/guideline/1822) (Appendix S3).

Discussion

Why does the panel issue weak recommendations?

Three reasons underlay the panel's judgement. First, the panel considered the net benefit of α-blockers across outcomes as small. The reduction in number of pain episodes was small, as was the absolute increase in stone clearance due to the high baseline risk of spontaneous stone clearance. Second, there was uncertainty about and variability of patients' values and preferences. The panel included two patients that helped to inform the likely patients' values and preferences in this setting but no further published empirical evidence was found on this topic. Third, there was uncertainty on the risk of MAEs due to the risk of bias and serious imprecision in these data. The panel weighted that as important as it was the only outcome on harms in the systematic review. For a substantial proportion of patients, the benefits might therefore not outweigh the uncertainty of the harms, although the possible MAEs are limited. The weak recommendation means shared decision-making to elicit individual patients' values and preferences is important in clinical practice.

Comparison with current guidelines

Most current guidelines advise the use of α-blockers (tamsulosin, doxazosin, terazosin, alfuzosin, naftopidil and silodosin) or the calcium-channel blocker nifedipine for MET of ureteric stones (Table 3).

They do not recommend corticosteroids as adjunct to α-blockers, nor as monotherapy. The recommendation in the present paper is based on the latest evidence and a process that adheres to international quality standards.

Strengths and limitations

It often takes years until potentially practice-changing evidence from a randomised trial is synthesised into a systematic review and incorporated into a clinical practice guideline, which is what clinicians need to make appropriate use of evidence in practice. Few guidelines provide a transparent and balanced view of potential benefits and harms of management alternatives to support shared decision-making between patients and clinicians [19]. The Rapid Recommendations procedure, which was followed for the development of these recommendations, represents an innovative approach where an international collaborative network of clinicians, researchers, methodologists and patient representatives will respond rapidly to potentially practice-changing evidence with updated systematic reviews and treatment recommendations developed according to standards for trustworthy guidelines.

The systematic review, upon which these recommendations are based, summarise the benefits and harms for patients with ureteric stones taking α-blockers. The guideline panel rated the quality of evidence for each outcome, judged the magnitude of these effects, and if there was there was variability in how patients might value the relative importance of the outcomes. All data were scrutinised using the GRADE framework and reported transparently. As GRADE makes clear to patients, clinicians and policy-makers on which arguments a decision was made, it therefore facilitates well-informed treatment choices [12].

The small number of patients on our panel is a limitation of the process, although three clinicians from the panel had ureteric stones in the past as well.

Implications for clinical practice

α-Blockers as MET is an off-label use of this drug class, and patients should be informed about this. The treatment duration in the RCTs of the systematic review was typically 4 weeks or until stone clearance. Tamsulosin was the most commonly prescribed α-blocker, given in a single dose of 0.4 mg/day.

The systematic review showed no difference between groups in MAEs. However, α-blockers may cause dizziness (often: ≥1/100 to <1/10 patients) and orthostatic hypotension (sometimes: ≥1/1000 to <1/100 patients), especially when combined with antihypertensive medication. Other possible AEs are ejaculation disorders (often), fatigue (sometimes), headache (sometimes), itch or a cutaneous rash (sometimes), and rarely floppy iris syndrome during operative cataract treatment [20].

One should be more cautious in the use of α-blockers in patients taking multiple medications because the use of α-blockers may increase the risk of drug–drug and drug–disease interactions in these patients.

α-Blockers are inexpensive. However, the overall impact on costs to the individual patient and the healthcare payer is uncertain when the consequences of each option are considered.

Fig. 1 Infographic. [Colour figure can be viewed at wileyonlinelibrary.com]

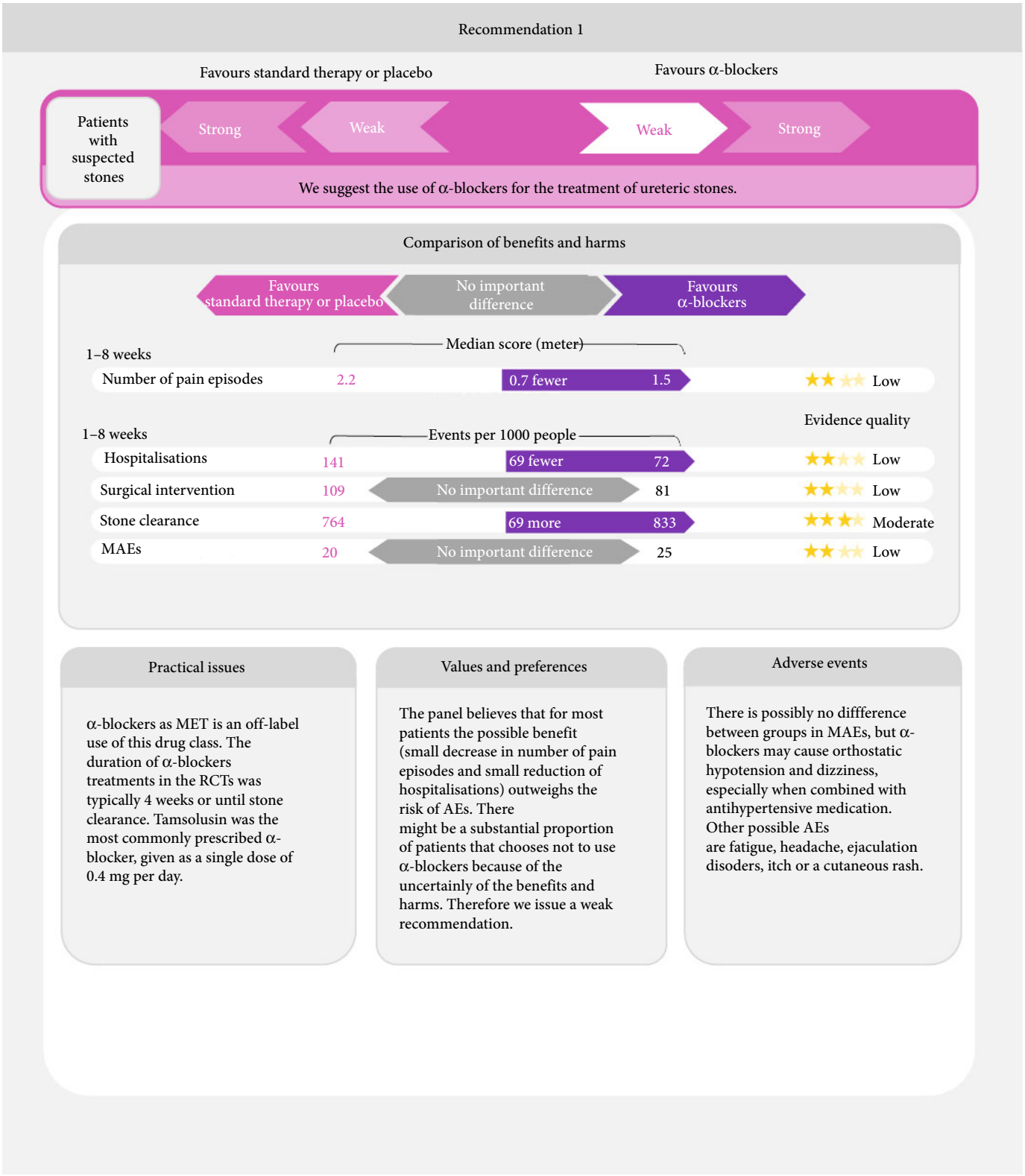

Table 3 Current guidelines for patients with ureteric stones.

Name	Target population	Guidance
EAU guidelines 2018 [21]	Urologists	Offer α-blockers as MET as one of the treatment options for (distal) ureteric stones >5 mm (strong)
AUA guidelines 2016 [22]	Urologists	Patients with uncomplicated ureteric stones ≤10 mm should be offered observation, and those with distal stones of similar size should be offered MET with α-blockers (strong)
EBM guidelines, 2017 [23]	Primary care physicians	α-blockers (either tamsulosin of alfuzosin) may be prescribed to facilitate passage of small (<5 mm) ureteric stone
UptoDate, 2016	Primary care physicians and urologists	We initiate treatment with tamsulosin (0.4 mg once daily) for 4 weeks to facilitate spontaneous stone passage in patients with stones ≤10 mm in diameter
NHG 2016 [6]	GPs	Tamsulosin is not recommended

EAU, European Association of Urology; EBM, Evidence-Based Medicine; NHG, Dutch College of General Practitioners.

Topics for further research

The treatment preferences and values of patients with ureteric stones is an area that needs future research. No studies were found that examined this topic.

Other topics for further research include the effect and safety profile of α-blockers in different populations, such as patients presenting at the emergency room vs GP practice, in older patients, or in patients with comorbidities.

Conflict of Interest

All authors have completed the International Committee of Medical Journal Editors (ICMJE) interests disclosure form and a detailed, contextualised description of all disclosures is reported in Appendix S1. The chair and methods editor judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised (by including maximal two-panel members with intellectual conflicts) as much as possible, whilst maintaining necessary expertise on the panel to make fully informed decisions.

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Abbreviations: (M)AE, (major) adverse event; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MET, medical expulsive therapy; RCT, randomised clinical trial; S.T.O.N.E., stone size (S), tract length (T), obstruction (O), number of involved calyces (N), and essence or stone density (E).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Panel members, role in guideline process and declaration of interest.
Appendix S2. Methodology for development of primary care Rapid Recommendations.
Appendix S3. All electronic multi-layered information available on the MAGICapp.

