Review Article

What Is the Role of α-Blockers for Medical Expulsive Therapy? Results From a Meta-analysis of 60 Randomized Trials and Over 9500 Patients

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Use of α-blockers for medical expulsive therapy (MET) has been the subject of huge debate in urology. Moreover, there have been a number of randomized controlled trials with differing results. We conducted a systematic review and meta-analysis of randomized controlled trials investigating the efficacy of α-blockers for MET. This review confirms there is a role for α-blockers in MET for ureteric stones specifically in stones >5 mm and distal ureteric stones, which is associated with improved stone expulsion. However, there is a slight increase in risk of nonsignificant side effects. UROLOGY ■■: ■■–■■, 2018. © 2018 Published by Elsevier Inc.

The incidence of urinary tract stones is between 1% and 15% worldwide and is increasing.[1,2] Although the majority of <1-cm stones pass spontaneously, this can take time and cause significant pain. The fastest treatment modality to achieve stone clearance is surgery. However, it is negated by both cost burden and potential risk to the patient. Therefore, urologists have attempted to treat stones more conservatively and tried various pharmacotherapies to facilitate passage. Subsequently, this gave the rise to medical expulsive therapy (MET).[3]

More so than any other class of medication, α-blockers have been shown to not only augment stone expulsion rates but also reduce the time to expulsion and pain.[4,5] Nonetheless, debate still goes on about its use, largely due to the sporadic rise of randomized controlled trials (RCTs) reporting their ineffectiveness.[6-8] However, these RCTs were met with a cohort of trials, which supported the role of α-blockers in MET.[9-14] This led to the publication of a number of reviews suggesting that α-blockers do have a role.[3-5,15-19] More recently, several trials of high quality have been published, which again have reported limited effect of α-blockers in increasing stone expulsion. Indeed, some have gone as far as to say refute the role of MET completely.[6-8,20]

To this end, we aimed to conduct a systematic review of the literature and a meta-analysis to include all RCTs reporting on α-blockers for MET. We aimed to assess its efficacy and safety.

METHODS

Search Strategy

The Cochrane methodology for systematic reviews was adopted to conduct this review.[21,22] The search strategy included the US National Library of Medicine's life science database (MEDLINE) (1980-November 2017), EMBASE (1980-November 2017), Cochrane Central Register of Controlled Trials—CENTRAL (in The Cochrane Library—2016), CINAHL (1980-November 2017), Clinicaltrials.gov, Google Scholar, and individual urologic journals.

Search terms used in conjunction with each other included "alpha blocker," "tamsulosin," "terazosin," "doxazosin," "alfuzosin," "silodosin," "urolithiasis," "urinary calculi," 'renal calculi," "ureteric calculi," "urinary stones," "Randomized controlled trial," and "medical expulsive therapy."

Medical Subject Headings (MeSH) phrases included:

- (("Adrenergic alpha-Antagonists" [MeSH]) AND ("Randomized Controlled Trial" [Publication Type]))

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- (("Adrenergic alpha-Antagonists" [MeSH]) AND ("Urinary Calculi"[MeSH]) AND "Randomized Controlled Trial" [Publication Type]))
- Same MeSH phrases as above, but replacing the class of medication with the individual drug name.

Study Selection and Data Extraction

All studies reporting on the use of an α-blocker compared with a control group in adult patients with ureteric stones of mean size (and SD) ≤10 mm were included. Abstract publications were excluded. Authors were contacted wherever the data were not available or not clear to adequately assess inclusion of their study.

Two authors independently identified studies eligible for inclusion and extracted the data accordingly. Both of these steps were verified by the senior author (OA). Disagreement between the authors was resolved by consensus of all authors.

Only studies using either a placebo or the hospital or country's protocol for conservative management (ie, analgesics, antispasmodics, hydration), serving as controls, were included. Studies on MET after treatments such as shock wave lithotripsy or ureteroscopy were only included if there were control and experimental arms, which had not undergone any other treatment for their stones.

The variables extracted included patient and stone demographics, expulsion rates, expulsion times, and side effect of the medication. The data of each study were pooled into a meta-analysis, in an intention-to-treat basis.

Statistical Analysis and Quality Assessment

We used the Review Manager (RevMan) v.5.2 program (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to conduct the analysis. For continuous data, a Mantel-Haenszel chi-square test was used and expressed as the mean difference (MD) with 95% confidence interval (CI), and for dichotomous data, an inverse variance was used and expressed as risk ratio (RR) with 95% CI. $P < .05$ was considered significant.[21,22] For numbers needed to treat (NNT) or harm, we used the GraphPad software (GraphPad Software, Inc., La Jolla, CA).

Heterogeneity was analyzed using a chi-square test on N − 1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test. I^2 values of 0%-40%, 30%-60%, 50%-90%, and 75%-100% indicate heterogeneity may not be important, moderate heterogeneity, substantial heterogeneity, and considerable heterogeneity.[21,22] A fixed-effects model was used unless statistically significant high heterogeneity (I^2 >75% was considered as significantly high heterogeneity) existed between studies. A random-effects model was employed if heterogeneity existed.[21,22]

An assessment of the methodological quality of the studies was conducted in line with the Cochrane handbook.[21,22] For quality assessment, the selection bias, performance bias, detection bias, attrition bias, and reporting bias were assessed in each of the included studies.

RESULTS

Literature Search

The literature search identified 1341 studies, of which 1189 were excluded due to nonrelevance based on titles and 51 were excluded due to lack of relevance based on review of the abstracts (Fig. 1). Full manuscripts were evaluated in 101 studies, of which 41 studies were excluded due to not meeting the inclusion criteria. The remaining 60 RCTs were included.[6-14,20,23-72]

Characteristics of the Included Studies

The trials spanned nearly 3 decades, the first being from 1994 with the latest in 2017. There was a total of 9517

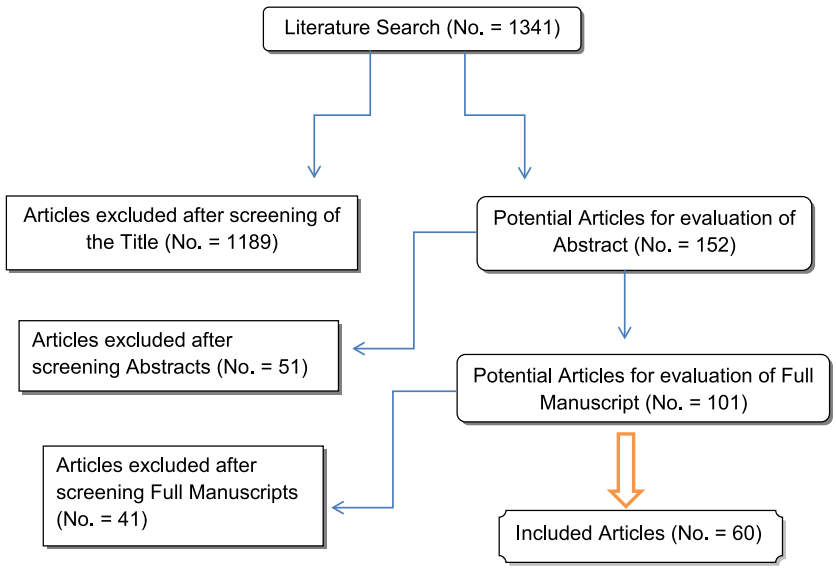


Figure 1. Flowchart for article selection process of the review. (Color version available online.)

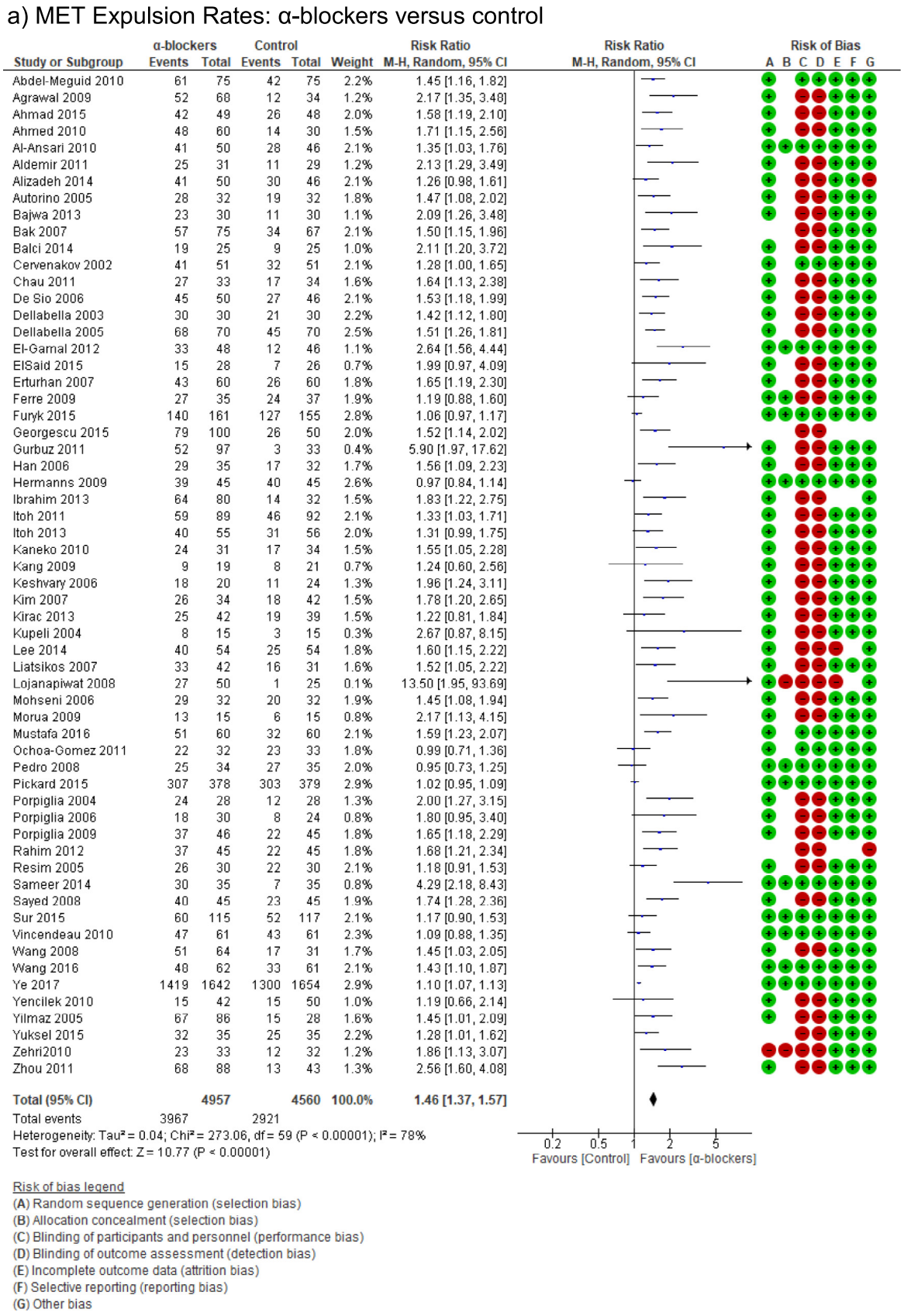


Figure 2. Medical expulsive therapy (MET) expulsion rates. CI, confidence interval. (Color version available online.)

patients: 4957 in the MET group and 4560 in the placebo group. The age range was between 17 and 74 years of age. Of the studies that mentioned sex, the male to female ratio was 1.3:1.

All studies compared an α-blocker with a controlled group. Thirty-five studies looked at tamsulosin 400 mcg (3630 patients), 7 studies on tamsulosin 200 mcg (469 patients), 8 studies on alfuzosin (488 patients), 4 studies on

b) MET Expulsion Rates: Subgroup analysis of Low risk of Bias studies: α-blockers versus control

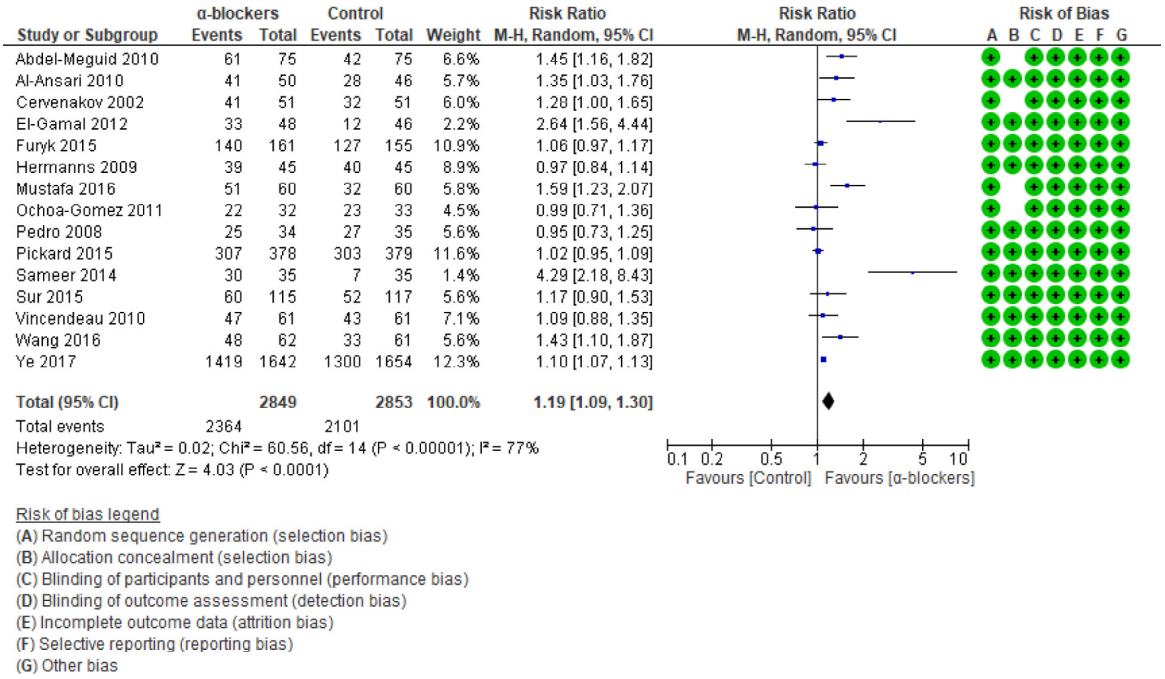


Fig. 2. Continued

doxazosin (260 patients), 4 studies on terazosin (247 patients), 6 studies on silodosin 200 mcg (817 patients).[6-14,20,23-72]

Supplementary Tables S1 and S2 depict the RCT patient and stone demographics and the primary and secondary outcomes, respectively. Figures 1 and 2 depict the studies that reported on the outcome measures for the primary and secondary outcomes of this review, where the data were extractable and poolable into a meta-analysis.

Meta-analysis Results

None of the RCTs have reported any difference between the MET and control groups regarding patients and stone demographics, and meta-analysis of the demographics confirms no significant difference: age (P = .78, MD: 0.07, 95% CI: −0.43, 0.57), sex (P = .70, RR: 1.02, 95% CI: 0.91, 1.15), or stone size (P = .08, MD: 0.06, 95% CI: −0.01, 0.12).

MET Efficacy

Primary Outcome. For MET efficacy measured by stone expulsion, for α-blockers vs control there was statistical significance favoring α-blockers (80% vs 64.1%) (P <.00001; RR: 1.46, 95% CI: 1.37, 1.57) (Fig. 2). Subanalyzing RCTs based on individual α-blockers found similar results, with statistical significance favoring individual α-blockers: tamsulosin 400 mcg (82.6% vs 68.7%) (P <.00001; RR: 1.41, 95% CI: 1.30, 1.54); tamsulosin 200 mcg (70.9% vs 43.1%) (P <.00001; RR: 1.64, 95% CI: 1.40, 1.93); alfuzosin (72.3% vs 33.5%) (P <.00001; RR: 2.16, 95% CI: 1.78, 2.61); doxazosin (72.1 vs 37.1%) (P <.00001; RR: 1.9, 95% CI: 1.49, 2.42); terazosin (73.2% vs 44.4%) (P <.00001; RR: 1.63, 95% CI: 1.33, 2.01); and silodosin (69% vs 51.8%) (P <.00001; RR: 1.33, 95% CI: 1.19, 1.49).

Secondary Outcomes. Meta-analysis of RCTs reporting these outcomes with extractable data has shown statistical significance favoring α-blockers in having a shorter time to expulsion as opposed to the control group (30 studies: 2824 patients) (P <.00001, MD: −3.39, 95% CI: −3.99, −2.79) (Fig. 3).

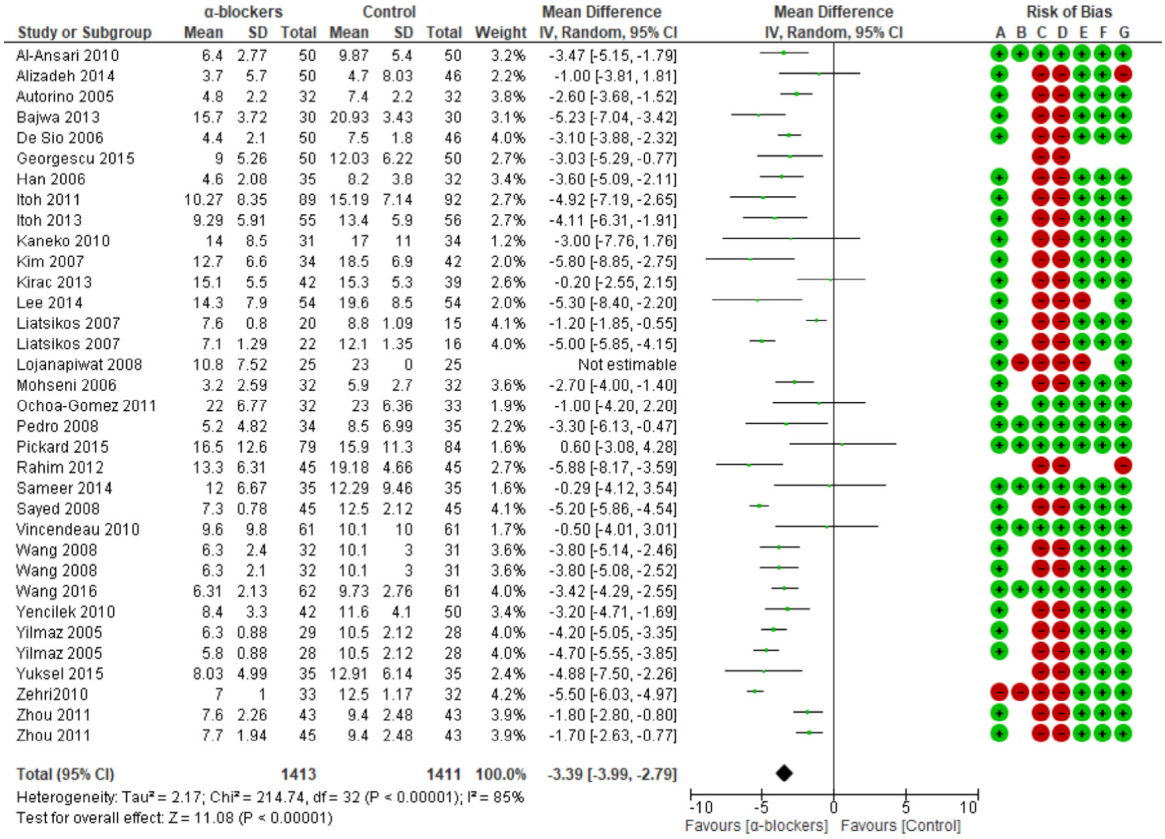
There was no statistical significance between the α-blocker and control groups in stones <5 mm (13 studies: 2380 patients) (84.7 vs 82.4%) (P = .13; RR: 1.03, 95% CI: 0.99, 1.06). There was statistical significance favoring α-blocker in stones >5 mm (18 studies: 3440 patients) (78.5% vs 62.6%) (P < .00001; RR: 1.28, 95% CI: 1.22, 1.33).

Regarding locality, analysis favored α-blocker for proximal ureteric stones (9 studies: 666 patients) (62.7% vs 47.9%) (P = .001; RR: 1.25, 95% CI: 1.09, 1.43). No difference was found between α-blocker and control groups for mid-ureteric stones (4 studies: 153 patients) (61.3% vs 61.5%) (P = .97; RR: 1, 95% CI: 0.79, 1.28). There was statistical significance favoring α-blocker for distal ureteric stones (58 studies: 8606 patients) (80.8% vs 65.1%) (P <.00001; RR: 1.44, 95% CI: 1.34, 1.54).

MET Safety

There was statistical significance showing more adverse events in the α-blocker group compared with the control group (28 studies: 6268 patients) (6.8% vs 3.5%) (P <.00001; RR: 1.83, 95% CI: 1.47, 2.28).

a) Time to Stone Expulsion



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

b) Stones <5mm

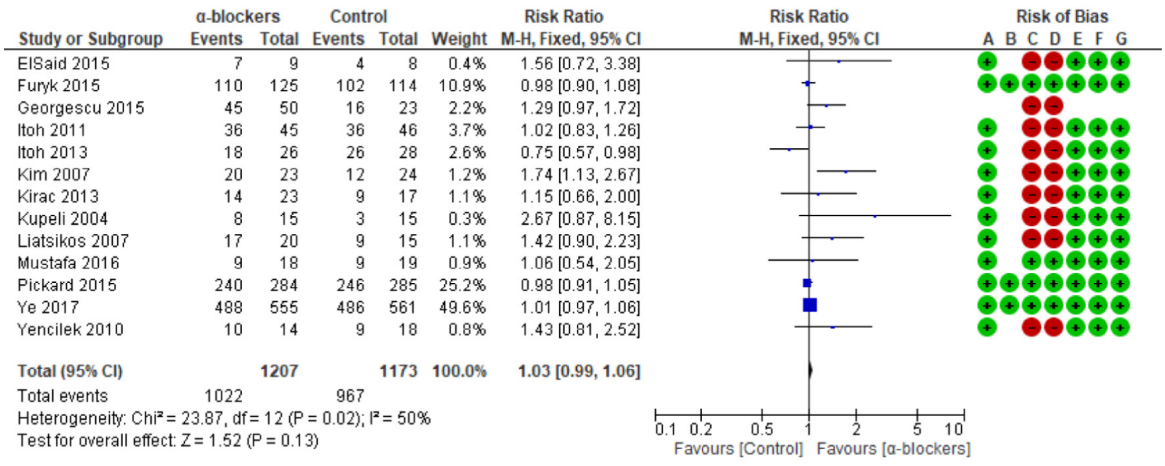

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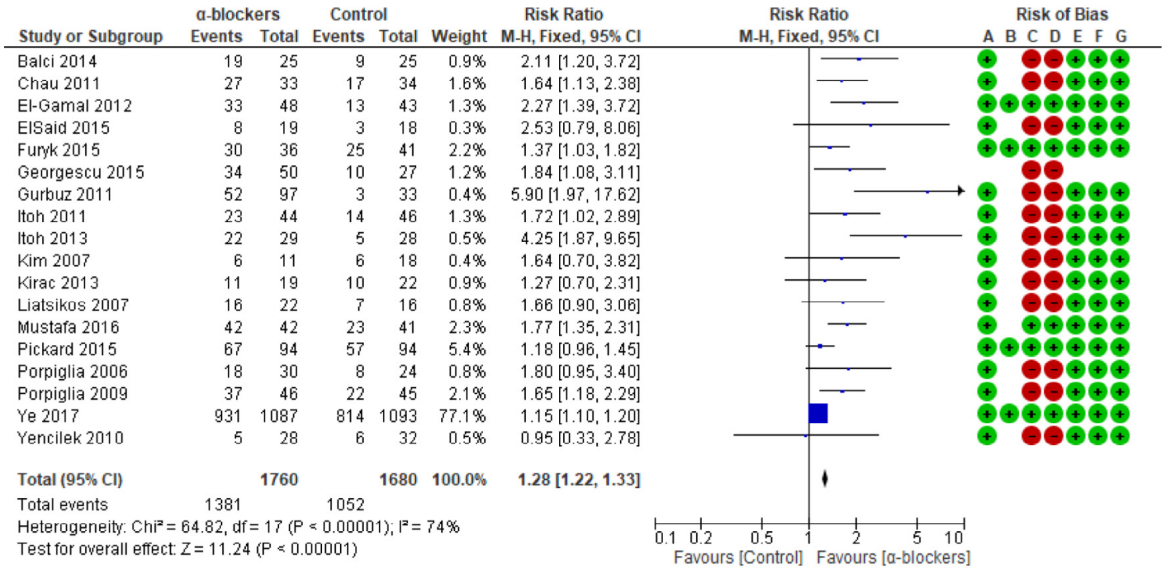
Figure 3. Secondary outcomes. CI, confidence interval. (Color version available online.)

c) Stones >5mm



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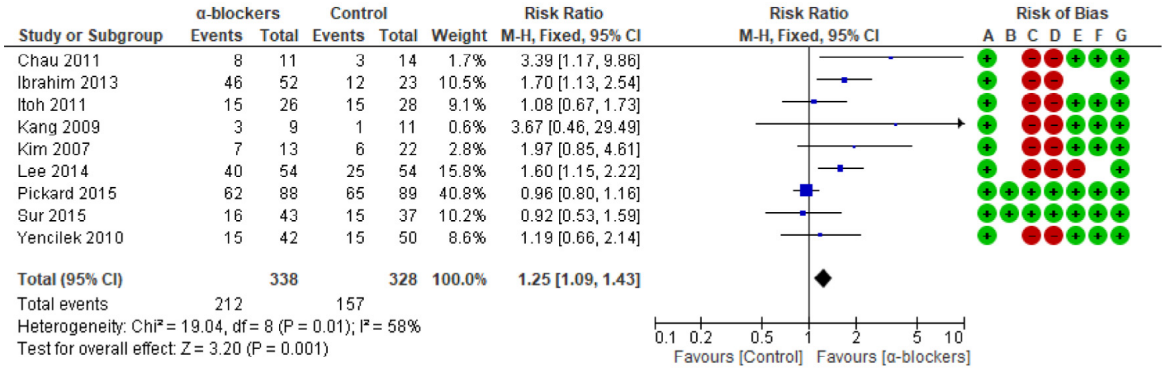
d) Proximal Ureter Stone Expulsion



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(G) Other bias

Fig. 3. Continued

There was statistical significance showing more rehospitalizations in the control group compared with the α-blocker group (16 studies: 1763 patients) (7% vs 17.5%) (*P* <.00001; RR: 0.43, 95% CI: 0.33, 0.56).

Numbers Needed to Treat

We calculated the NNT to establish a better understanding of each subcategory or group. For all α-blockers, the NNT was 1 in 7, with an absolute risk reduction (ARR) of 15.97% (95% CI 14.19%-17.75%).

For stones <5 mm in size, the NNH was 1 in 45, with an ARR of 2.23% (95% CI −0.74% to 5.21%). As the 95%CI for the ARR extends from a negative number, there is a risk to do harm with treatment.[73] For stones >5 mm in size, the NNT was 1 in 7, with an ARR of 15.85% (95% CI 12.84%-18.85%).

For proximal stones, the NNT was 1 in 7, with an ARR of 14.86% (95% CI 7.39%-22.3%). For mid-stones, the NNH was 1 in 488, with an absolute risk increase of 0.21% (95%CI −15.2% to 15.6%). As the 95%CI for the ARR

e) Mid Ureter Stone Expulsion

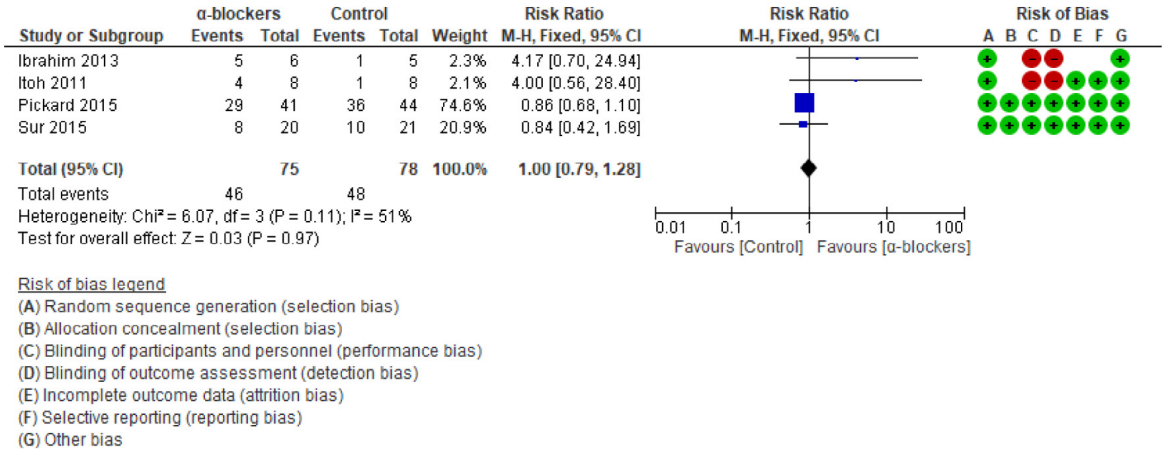


Fig. 3. Continued

extends from a negative number, there is a risk to do harm with treatment.[73] For distal stones, the NNT was 1 in 7, with an ARR of 15.68% (95% CI 13.82%-17.53%).

Methodological Quality Assessment

All of the studies were RCTs and therefore were considered of high quality. However, the majority of the trials had a high risk of bias. Supplementary Figure S1 depicts the summary of the quality assessment based on the reviewing authors' judgment of risks of bias for each included study.

We found that the blinding was the main differential aspect of the quality assessment between the studies, with 15 studies that double blinded their trial.[6-14,20,37,63,65,71,72] Therefore, we conducted a further subanalysis of these trials.

Taking into consideration only low risk of bias studies, there was no difference with the final result, favoring α-blockers to increase stone expulsion rates (15 studies: 5702 patients) (83% vs 73.6%) (P <.0001; RR: 1.19, 95% CI: 1.09, 1.30).

The results were similar for the subgroup analysis favoring α-blockers for a shorter time to expulsion (7 studies: 712 patients) (P <.00001, MD: −2.92, 95% CI: −3.61, −2.23), increase in expulsion rates for stones >5 mm (84.1% vs 70.8%) (5 studies: 2627 patients) (P = .002, RR: 1.39, 95% CI: 1.13, 1.71), and increase in expulsion rates for distal ureteric stones (84.6% vs 74.2%) (15 studies: 5319 patients) (P < 0001, RR: 1.22, 95% CI: 1.11, 1.33).

DISCUSSION

Summary of Meta-analysis

As the main goal of this review was to establish the efficacy of MET, we analyzed all RCTs comparing α-blockers with a control group. Pooled analysis would suggest that α-blockers (and individual α-blockers) do have a role in MET.

Analysis of secondary outcome measures has demonstrated that use of α-blockers led to a shorter time to expulsion of stones. Furthermore, the α-blockers were beneficial for proximally and distally located stones and stones >5 mm in size. They also reduced readmission to hospital due to pain after initial discharge. This was reflective of the narrow NNT for each outcome.

However, as the main criticism for MET throughout the years was lack of trials with low risk of bias, we scrutinized these trials based on risk of bias. We found only 22% of the RCTs (13/58) to have low risk of bias. Subanalysis of these trials revealed similar results to the whole analyses, except the lack of benefit of α-blockers for proximal ureteric stones.

These findings are consistent with basic science research studies showing that relaxation of the smooth muscles in the ureter increases stone expulsion.[74-79] By the effect of α-blockers relaxing ureter smooth muscles with the continual build-up of pressure above the stone, expulsion of the stone is more likely to occur.[5,15-19,74-79] This was also demonstrated in our review as MET was found to increase the expulsion rate of stones >5 mm as opposed to those <5 mm where no benefit was found in addition to reducing time until stone expulsion. Lastly, as α-receptors are predominantly found in the distal ureter, stone expulsion rates were higher in the MET groups in the distal ureter, whereas no difference was found in the mid or proximal ureter compared with control groups.[76]

Although there were no major side effects that caused significant mortality or morbidity to any of the patients, the α-blocker groups did have significantly more side effects. Of note, however, use of an α-blocker did lead to a reduced rehospitalization rate. Adverse events recorded by each study have been listed in Supplementary Table S2. There was a large dependency on how these complications were reported by different studies, and as a result, the authors of this review were unable to perform a pooled analysis of individual complications.

f) Distal Ureter Stone Expulsion

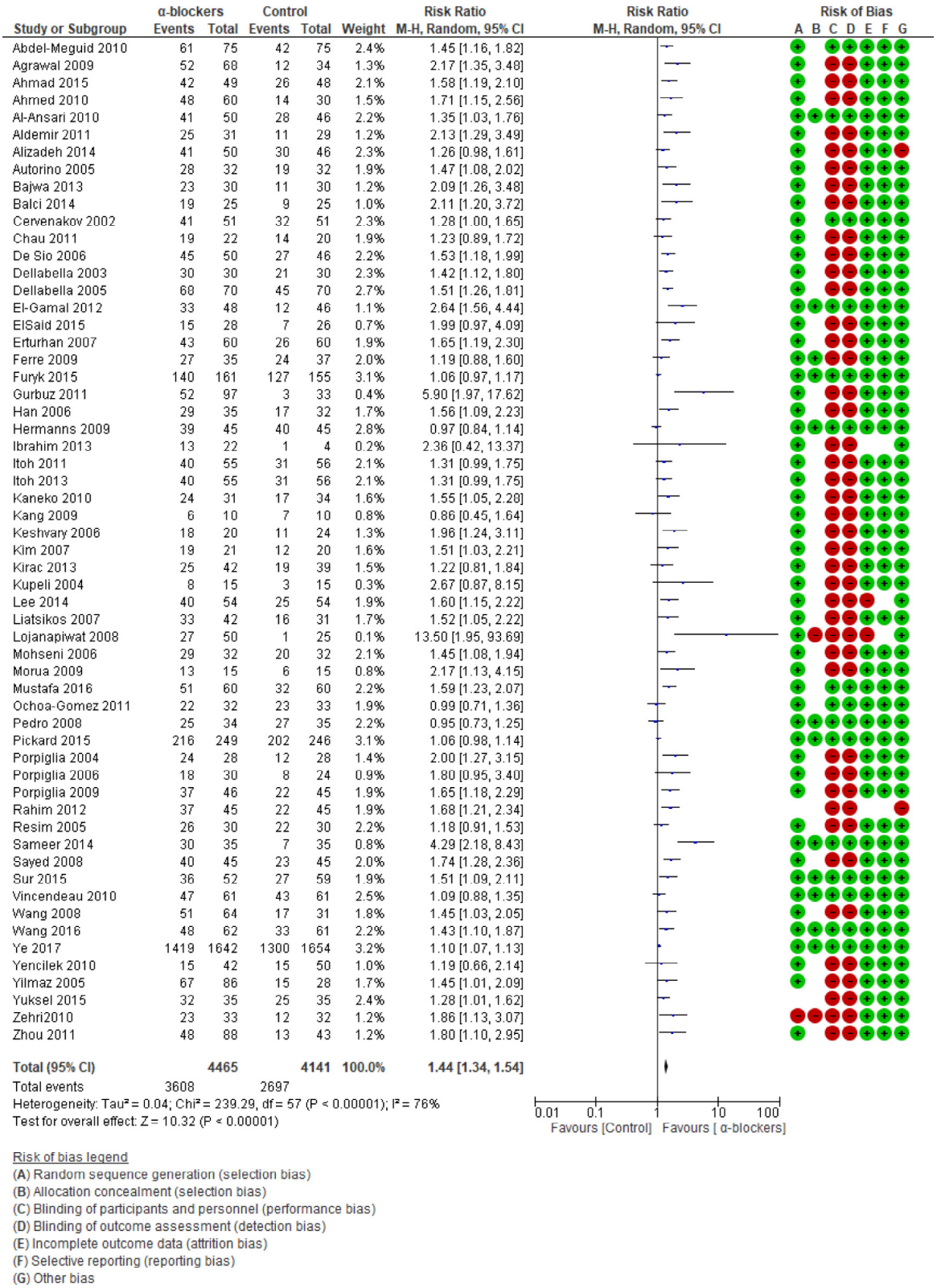
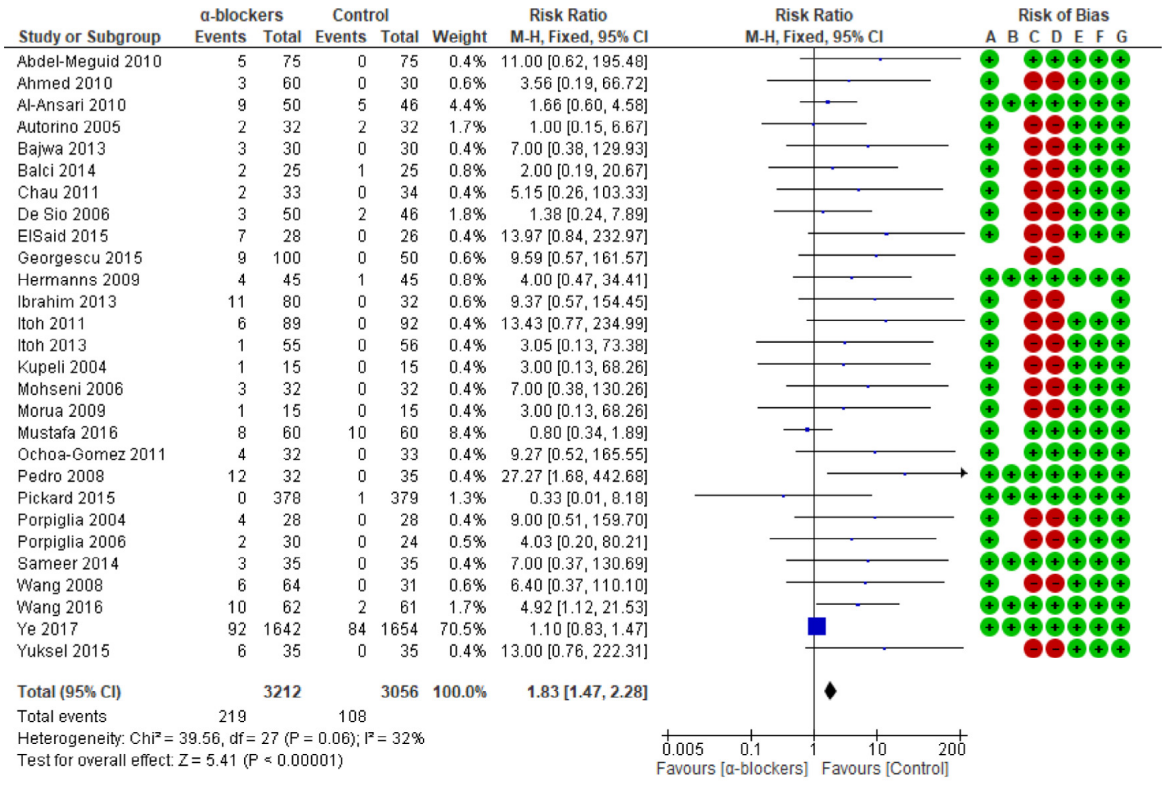


Fig. 3. Continued

Similarities and Differences Compared With Other Systematic Reviews

Seven meta-analyses have been published within the last 10 years looking at the efficacy of MET.[4,5,15-19] These studies addressed use of α-blockers in general and determined that they do have a role in MET to facilitate stone passage.[4,5,16,17,19] Two reviews found that the use of indivisible α-blockers, alfuzosin or silodosin, is also effective

g) Side Effects per patients



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h) Re-Hospitalisation rates

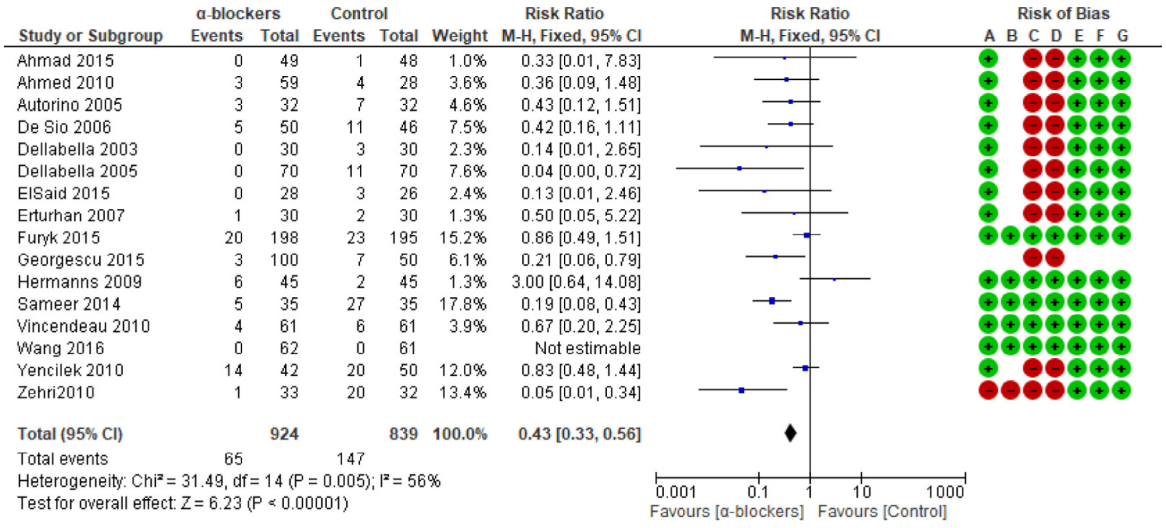

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Fig. 3. Continued

in increasing stone passage.[15,18] Our review mirrors previous reviews in that we have also confirmed the importance of α-blockers in MET.

The key difference and therefore strength of our review is the methodological approach we have taken. Importantly, the decision was made not to include published abstracts, which would have rendered detailed scrutiny very difficult and presented challenges with incomplete data sets and introduced bias accordingly.[4,5,16-19] Careful review of previous meta-analyses reveals subtle inconsistencies relating to inclusion criteria. For example, a recent published review included a non-RCT into their study.[4,80] Lastly, even the Cochrane review published had areas for improvement.[17] The authors had extracted data results from the trials and included them into the pooled analysis. From a methodological perspective, this is considered suboptimal. In addition to this, certain trials were excluded, which arguably should have been included.

Strengths and Limitations of This Review

A major strength of our review is that we adhered closely to the Cochrane methodology. Moreover, we have included an up-to-date literature search of all trials found in the most commonly used bibliographic databases that compared the use of an α-blocker to a control group. Furthermore, we have calculated an NNT figure to best aid clinicians understand the benefit in the use of α-blockers or lack of it for each category. This review has also analyzed individual α-blocker results to get a better understanding of the individual α-blocker role.

As will all things man has made, this review is not without limitations. Like previous reviews, the main limitation of ours was the inclusion of a range of studies with different levels of risk of bias. However, we included a subgroup analysis excluding high-risk studies, which is a further strength of this review compared with others. Although no difference was found between α-blocker and control groups for mid-ureteric stones, this lack of effect could possibly be related to the limited number of studies (n = 4).

Implications for Research and Practice

This review has ratified that there is a benefit for the use of α-blockers as part of the MET strategy and we recommend its use, especially for stones >5 mm and in the distal ureter accordingly. Focus of future research should be on looking at the subgroups to which these benefits can be applied. These include men vs women, young vs elderly, stone sizes, stone location, and pain relief. This should be in addition to patients with multiple stones and post-treated stones, for example, benefits of α-blockers post-ESWL.

CONCLUSION

Pooled analysis of RCTs would suggest that α-blockers increase stone expulsion rates (80% vs 64.1%, P <.00001). Their role might be more significant for larger (>5 mm) stones (78.5% vs 62.6%, P <.00001) and stones in the lower ureter (80.8% vs 65.1%, P <.00001). Furthermore, MET was associated with more side effects (6.8% vs 3.5%, P <.00001) albeit not severe; however, it lessened rehospitalization rates (7% vs 17.5%, P <.00001).

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.03.028.