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

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Use of  $\alpha$ -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  $\alpha$ -blockers for MET. This review confirms there is a role for  $\alpha$ -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

The incidence of urinary tract stones is between 1% and 15% worldwide and is increasing.<sup>1,2</sup> 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).<sup>3</sup>

More so than any other class of medication,  $\alpha$ -blockers have been shown to not only augment stone expulsion rates but also reduce the time to expulsion and pain.<sup>4,5</sup> Nonetheless, debate still goes on about its use, largely due to the sporadic rise of randomized controlled trials (RCTs) reporting their ineffectiveness.<sup>68</sup> However, these RCTs were met with a cohort of trials, which supported the role of  $\alpha$ -blockers in MET.<sup>9.14</sup> This led to the publication of a number of reviews suggest-

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ing that  $\alpha$ -blockers do have a role.<sup>3-5,15-19</sup> More recently, several trials of high quality have been published, which again have reported limited effect of  $\alpha$ -blockers in increasing stone expulsion. Indeed, some have gone as far as to say refute the role of MET completely.<sup>6-8,20</sup>

To this end, we aimed to conduct a systematic review of the literature and a meta-analysis to include all RCTs reporting on  $\alpha$ -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.<sup>21,22</sup> 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  $\alpha$ -blocker compared with a control group in adult patients with ureteric stones of mean size (and SD)  $\leq 10$  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.<sup>21,22</sup> 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<sup>2</sup> test. I<sup>2</sup> values of 0%-40%, 30%-60%, 50%-90%, and 75%-100% indicate heterogeneity may not be important, moderate heterogeneity, substantial heterogeneity, and considerable heterogeneity.<sup>21,22</sup> A fixed-effects model was used unless statistically significant high heterogeneity) existed between studies. A random-effects model was employed if heterogeneity existed.<sup>21,22</sup>

An assessment of the methodological quality of the studies was conducted in line with the Cochrane handbook.<sup>21,22</sup> 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.<sup>6-14,20,23-72</sup>

### **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

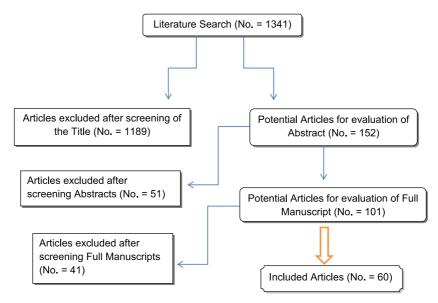


Figure 1. Flowchart for article selection process of the review. (Color version available online.)

# a) MET Expulsion Rates: α-blockers versus control

<i>,</i> .	a-ploci	kers	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Abdel-Meguid 2010	61	75	42	75	2.2%	1.45 [1.16, 1.82]		
Agrawal 2009	52	68	12	34	1.2%	2.17 [1.35, 3.48]		
Ahmad 2015 Ahmed 2010	42 48	49 60	26 14	48 30	2.0%	1.58 [1.19, 2.10]		
Al-Ansari 2010	40	50	28	30 46	1.5% 2.1%	1.71 [1.15, 2.56] 1.35 [1.03, 1.76]		
Aldemir 2011	25	31	11	29	1.2%	2.13 [1.29, 3.49]		
Alizadeh 2014	41	50	30	46	2.1%	1.26 [0.98, 1.61]		
Autorino 2005	28	32	19	32	1.8%	1.47 [1.08, 2.02]		
Bajwa 2013	23	30	11	30	1.1%	2.09 [1.26, 3.48]	——	
Bak 2007	57	75	34	67	2.1%	1.50 [1.15, 1.96]		
Balci 2014	19	25	9	25	1.0%	2.11 [1.20, 3.72]	———	• •••••
Cervenakov 2002	41	51	32	51	2.1%	1.28 [1.00, 1.65]		
Chau 2011	27	33	17	34	1.6%	1.64 [1.13, 2.38]		• •••••
De Sio 2006	45	50	27	46	2.1%	1.53 [1.18, 1.99]		• •••••
Dellabella 2003	30	30	21	30	2.2%	1.42 [1.12, 1.80]		
Dellabella 2005 El-Gamal 2012	68 33	70 48	45 12	70 46	2.5% 1.1%	1.51 [1.26, 1.81] 2.64 [1.56, 4.44]		
ElSaid 2015	15	28	7	26	0.7%	1.99 [0.97, 4.09]		
Erturhan 2007	43	60	26	60	1.8%	1.65 [1.19, 2.30]		
Ferre 2009	27	35	24	37	1.9%	1.19 [0.88, 1.60]	+	
Furyk 2015	140	161	127	155	2.8%	1.06 [0.97, 1.17]	+	
Georgescu 2015	79	100	26	50	2.0%	1.52 [1.14, 2.02]		
Gurbuz 2011	52	97	3	33	0.4%	5.90 [1.97, 17.62]		
Han 2006	29	35	17	32	1.7%	1.56 [1.09, 2.23]		
Hermanns 2009	39	45	40	45	2.6%	0.97 [0.84, 1.14]	+	
Ibrahim 2013	64	80	14	32	1.5%	1.83 [1.22, 2.75]	<del></del>	
ltoh 2011	59	89	46	92	2.1%	1.33 [1.03, 1.71]		• • • • • • •
Itoh 2013	40	55	31	56	2.0%	1.31 [0.99, 1.75]		• •••••
Kaneko 2010 Kana 2000	24	31	17	34	1.5%	1.55 [1.05, 2.28]		
Kang 2009 Kachyany 2006	9 18	19 20	8 11	21 24	0.7% 1.3%	1.24 [0.60, 2.56]		
Keshvary 2006 Kim 2007	26	34	18	42	1.5%	1.96 [1.24, 3.11] 1.78 [1.20, 2.65]		
Kirac 2013	25	42	19	39	1.5%	1.22 [0.81, 1.84]		
Kupeli 2004	8	15	3	15	0.3%	2.67 [0.87, 8.15]		
Lee 2014	40	54	25	54	1.8%	1.60 [1.15, 2.22]		
Liatsikos 2007	33	42	16	31	1.6%	1.52 [1.05, 2.22]		
Lojanapiwat 2008	27	50	1	25	0.1%	13.50 [1.95, 93.69]	│	•••••
Mohseni 2006	29	32	20	32	1.9%	1.45 [1.08, 1.94]		• •••••
Morua 2009	13	15	6	15	0.8%	2.17 [1.13, 4.15]		
Mustafa 2016	51	60	32	60	2.1%	1.59 [1.23, 2.07]		
Ochoa-Gomez 2011	22	32	23	33	1.8%	0.99 [0.71, 1.36]		
Pedro 2008	25	34	27	35	2.0%	0.95 [0.73, 1.25]		
Pickard 2015 Perpidia 2004	307 24	378 28	303 12	379 28	2.9%	1.02 [0.95, 1.09]		
Porpiglia 2004 Porpiglia 2006	24 18	20 30	8	20	1.3% 0.8%	2.00 [1.27, 3.15] 1.80 [0.95, 3.40]		
Porpiglia 2009	37	46	22	45	1.8%	1.65 [1.18, 2.29]		
Rahim 2012	37	45	22	45	1.8%	1.68 [1.21, 2.34]		00 0
Resim 2005	26	30	22	30	2.1%	1.18 [0.91, 1.53]	+	
Sameer 2014	30	35	7	35	0.8%	4.29 [2.18, 8.43]		
Sayed 2008	40	45	23	45	1.9%	1.74 [1.28, 2.36]	<del></del>	
Sur 2015	60	115	52	117	2.1%	1.17 [0.90, 1.53]	+	
Vincendeau 2010	47	61	43	61	2.3%	1.09 [0.88, 1.35]	+-	
Wang 2008	51	64	17	31	1.7%	1.45 [1.03, 2.05]		
Wang 2016	48	62	33	61	2.1%	1.43 [1.10, 1.87]		
Ye 2017	1419		1300	1654	2.9%	1.10 [1.07, 1.13]		
Yencilek 2010	15	42	15	50	1.0%	1.19 [0.66, 2.14]		
Yilmaz 2005 Yukeel 2015	67 22	86 26	15	28	1.6%	1.45 [1.01, 2.09]		
Yuksel 2015 Zehri2010	32 23	35 33	25 12	35 32	2.2% 1.2%	1.28 [1.01, 1.62] 1.86 [1.13, 3.07]		
Zhou 2011	23	33 88	12	32 43	1.2%	1.86 [1.13, 3.07] 2.56 [1.60, 4.08]		
2.104.2011	00	00	13	40	1.370	2.50 [1.00, 4.00]		
Total (95% CI)		4957		4560	100.0%	1.46 [1.37, 1.57]	•	
Total events	3967		2921					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.04; Chi <sup>a</sup>		06, df = 5	9 (P < I	0.00001);	I² = 78%	0.2 0.5 1 2 5 Favours [Control] Favours [α-blockers]	
Risk of bias legend (A) Random sequenc (B) Allocation conceal (C) Blinding of particip (D) Blinding of outcom (E) Incomplete outcon	e generati ment (sel ants and ne assess	on (sel ection b personi ment (c	ection bia bias) nel (perfo detection	rmanc	e bias)		Favours (Control) - Favours (C-DIOCKefs)	
(F) Selective reporting (G) Other bias								

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  $\alpha$ -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: $\alpha$ -blockers versus control

	a-ploci	kers	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Abdel-Meguid 2010	61	75	42	75	6.6%	1.45 [1.16, 1.82]		
Al-Ansari 2010	41	50	28	46	5.7%	1.35 [1.03, 1.76]	_ <b></b>	
Cervenakov 2002	41	51	32	51	6.0%	1.28 [1.00, 1.65]		
El-Gamal 2012	33	48	12	46	2.2%	2.64 [1.56, 4.44]		
Furyk 2015	140	161	127	155	10.9%	1.06 [0.97, 1.17]	+	
Hermanns 2009	39	45	40	45	8.9%	0.97 [0.84, 1.14]	-	
Mustafa 2016	51	60	32	60	5.8%	1.59 [1.23, 2.07]		
Ochoa-Gomez 2011	22	32	23	33	4.5%	0.99 [0.71, 1.36]	-+-	
Pedro 2008	25	34	27	35	5.6%	0.95 [0.73, 1.25]		
Pickard 2015	307	378	303	379	11.6%	1.02 [0.95, 1.09]	+	
Sameer 2014	30	35	7	35	1.4%	4.29 [2.18, 8.43]		
Sur 2015	60	115	52	117	5.6%	1.17 [0.90, 1.53]	+	
Vincendeau 2010	47	61	43	61	7.1%	1.09 [0.88, 1.35]	- <del>-</del>	
Wang 2016	48	62	33	61	5.6%	1.43 [1.10, 1.87]		
Ye 2017	1419	1642	1300	1654	12.3%	1.10 [1.07, 1.13]	-	
Total (95% CI)		2849		2853	100.0%	1.19 [1.09, 1.30]	•	
Total events	2364		2101				-	
Heterogeneity: Tau <sup>2</sup> =	0.02; Chi <sup>a</sup>	<sup>2</sup> = 60.5	6, df = 14	(P ≤ 0.	00001); P	²= 77%		
Test for overall effect: J							0.1 0.2 0.5 1 2 5 10	
							Favours [Control] Favours [a-blockers]	
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Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

(F) Selective reportil (G) Other bias

Fig. 2. Continued

doxazosin (260 patients), 4 studies on terazosin (247 patients), 6 studies on silodosin 200 mcg (817 patients).<sup>6-14,20,23-72</sup>

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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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

	α-b	locker	s	С	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% C	I ABCDEFG
Al-Ansari 2010	6.4	2.77	50	9.87	5.4	50	3.2%	-3.47 [-5.15, -1.79]		
Alizadeh 2014	3.7	5.7	50	4.7	8.03	46	2.2%	-1.00 [-3.81, 1.81]		
Autorino 2005	4.8	2.2	32	7.4	2.2	32	3.8%	-2.60 [-3.68, -1.52]		
Bajwa 2013	15.7	3.72	30	20.93	3.43	30	3.1%	-5.23 [-7.04, -3.42]		
De Sio 2006	4.4	2.1	50	7.5	1.8	46	4.0%	-3.10 [-3.88, -2.32]	-	
Georgescu 2015	9	5.26	50	12.03	6.22	50	2.7%	-3.03 [-5.29, -0.77]		••
Han 2006	4.6	2.08	35	8.2	3.8	32	3.4%	-3.60 [-5.09, -2.11]	_ <b>—</b>	
Itoh 2011	10.27	8.35	89	15.19	7.14	92	2.7%	-4.92 [-7.19, -2.65]		
Itoh 2013	9.29	5.91	55	13.4	5.9	56	2.7%	-4.11 [-6.31, -1.91]		
Kaneko 2010	14	8.5	31	17	11	34	1.2%	-3.00 [-7.76, 1.76]		
Kim 2007	12.7	6.6	34	18.5	6.9	42	2.0%	-5.80 [-8.85, -2.75]		
Kirac 2013	15.1	5.5	42	15.3	5.3	39	2.6%	-0.20 [-2.55, 2.15]		
Lee 2014	14.3	7.9	54	19.6	8.5	54	2.0%	-5.30 [-8.40, -2.20]		$\bullet$ $\bullet \bullet \bullet$ $\bullet$
Liatsikos 2007	7.6	0.8	20	8.8	1.09	15	4.1%	-1.20 [-1.85, -0.55]		
Liatsikos 2007	7.1	1.29	22	12.1	1.35	16	4.0%	-5.00 [-5.85, -4.15]		
Lojanapiwat 2008	10.8	7.52	25	23	0	25		Not estimable		
Mohseni 2006	3.2	2.59	32	5.9	2.7	32	3.6%	-2.70 [-4.00, -1.40]		
Ochoa-Gomez 2011	22	6.77	32	23	6.36	33	1.9%	-1.00 [-4.20, 2.20]		
Pedro 2008	5.2	4.82	34	8.5	6.99	35	2.2%	-3.30 [-6.13, -0.47]		
Pickard 2015	16.5	12.6	79	15.9	11.3	84	1.6%	0.60 [-3.08, 4.28]		
Rahim 2012	13.3	6.31	45	19.18	4.66	45	2.7%	-5.88 [-8.17, -3.59]		•• •
Sameer 2014	12	6.67	35	12.29	9.46	35	1.6%	-0.29 [-4.12, 3.54]		
Sayed 2008	7.3	0.78	45	12.5	2.12	45	4.1%	-5.20 [-5.86, -4.54]	-	
Vincendeau 2010	9.6	9.8	61	10.1	10	61	1.7%	-0.50 [-4.01, 3.01]		
Wang 2008	6.3	2.4	32	10.1	3	31	3.6%	-3.80 [-5.14, -2.46]	<u> </u>	
Wang 2008	6.3	2.1	32	10.1	3	31	3.6%	-3.80 [-5.08, -2.52]	<u> </u>	
Wang 2016	6.31	2.13	62	9.73	2.76	61	4.0%	-3.42 [-4.29, -2.55]		
Yencilek 2010	8.4	3.3	42	11.6	4.1	50	3.4%	-3.20 [-4.71, -1.69]		
Yilmaz 2005	6.3	0.88	29	10.5	2.12	28	4.0%	-4.20 [-5.05, -3.35]	-	
Yilmaz 2005	5.8	0.88	28	10.5	2.12	28	4.0%	-4.70 [-5.55, -3.85]	-	
Yuksel 2015	8.03	4.99	35	12.91	6.14	35	2.4%	-4.88 [-7.50, -2.26]		
Zehri2010	7	1	33	12.5	1.17	32	4.2%	-5.50 [-6.03, -4.97]	-	
Zhou 2011	7.6	2.26	43	9.4	2.48	43	3.9%	-1.80 [-2.80, -0.80]		
Zhou 2011		1.94	45	0.4	2.48	43	3.9%	-1.70 [-2.63, -0.77]		
	7.7	1.94	40	9.4	2.40	40	0.070	-1.10[-2.00,-0.11]		• ••••
Total (95% CI)	7.7	1.94	40 1413	9.4	2.40		100.0%	-3.39 [-3.99, -2.79]		• •••••

Heterogeneity: Tau² = 2.17; Chi² = 214.74, df = 32 (P < 0.00001); i² = 85% Test for overall effect: Z = 11.08 (P < 0.00001)



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

# b) Stones <5mm

	a-plock	(ers	Contr	ol		Risk Ratio	Risk Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
EISaid 2015	7	9	4	8	0.4%	1.56 [0.72, 3.38]		
Furyk 2015	110	125	102	114	10.9%	0.98 [0.90, 1.08]	+	
Georgescu 2015	45	50	16	23	2.2%	1.29 [0.97, 1.72]	<u> </u>	••
Itoh 2011	36	45	36	46	3.7%	1.02 [0.83, 1.26]	+	$\bullet  \bullet \bullet \bullet \bullet \bullet \bullet$
Itoh 2013	18	26	26	28	2.6%	0.75 [0.57, 0.98]		• •••••
Kim 2007	20	23	12	24	1.2%	1.74 [1.13, 2.67]		$\bullet  \bullet \bullet \bullet \bullet \bullet \bullet$
Kirac 2013	14	23	9	17	1.1%	1.15 [0.66, 2.00]	_ <del></del>	• •••••
Kupeli 2004	8	15	3	15	0.3%	2.67 [0.87, 8.15]		$\bullet$ $\bullet \bullet \bullet \bullet \bullet \bullet$
Liatsikos 2007	17	20	9	15	1.1%	1.42 [0.90, 2.23]	+	$\bullet  \bullet \bullet \bullet \bullet \bullet \bullet$
Mustafa 2016	9	18	9	19	0.9%	1.06 [0.54, 2.05]		$\bullet  \bullet \bullet \bullet \bullet \bullet \bullet$
Pickard 2015	240	284	246	285	25.2%	0.98 [0.91, 1.05]	+	
Ye 2017	488	555	486	561	49.6%	1.01 [0.97, 1.06]	<b></b>	
Yencilek 2010	10	14	9	18	0.8%	1.43 [0.81, 2.52]	+	$\bullet  \bullet \bullet \bullet \bullet \bullet \bullet$
Total (95% CI)		1207		1173	100.0%	1.03 [0.99, 1.06]	•	
Total events	1022		967					
Heterogeneity: Chi <sup>2</sup> =	23.87, df	= 12 (P	= 0.02);	r = 509	6			1
Test for overall effect:	Z=1.52 (	(P = 0.1	3)				0.1 0.2 0.5 1 2 5 10 Favours [Control] Favours [α-blockers	;]
Risk of bias legend								1

Risk of blas legend (A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias



## c) Stones >5mm

	a-ploct	kers	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG
Balci 2014	19	25	9	25	0.9%	2.11 [1.20, 3.72]		• ••••
Chau 2011	27	33	17	34	1.6%	1.64 [1.13, 2.38]		• •••••
El-Gamal 2012	33	48	13	43	1.3%	2.27 [1.39, 3.72]		
ElSaid 2015	8	19	3	18	0.3%	2.53 [0.79, 8.06]		• •••••
Furyk 2015	30	36	25	41	2.2%	1.37 [1.03, 1.82]		
Georgescu 2015	34	50	10	27	1.2%	1.84 [1.08, 3.11]		••
Gurbuz 2011	52	97	3	33	0.4%	5.90 [1.97, 17.62]		
Itoh 2011	23	44	14	46	1.3%	1.72 [1.02, 2.89]		• •••••
Itoh 2013	22	29	5	28	0.5%	4.25 [1.87, 9.65]	· · · · · · · · · · · · · · · · · · ·	- • •••••
Kim 2007	6	11	6	18	0.4%	1.64 [0.70, 3.82]		• •••••
Kirac 2013	11	19	10	22	0.9%	1.27 [0.70, 2.31]		• •••••
Liatsikos 2007	16	22	7	16	0.8%	1.66 [0.90, 3.06]		• •••••
Mustafa 2016	42	42	23	41	2.3%	1.77 [1.35, 2.31]		$\bullet$ $\bullet \bullet \bullet \bullet \bullet \bullet$
Pickard 2015	67	94	57	94	5.4%	1.18 [0.96, 1.45]		
Porpiglia 2006	18	30	8	24	0.8%	1.80 [0.95, 3.40]		
Porpiglia 2009	37	46	22	45	2.1%	1.65 [1.18, 2.29]		
Ye 2017	931	1087	814	1093	77.1%	1.15 [1.10, 1.20]		
Yencilek 2010	5	28	6	32	0.5%	0.95 [0.33, 2.78]		• •••••
Total (95% CI)		1760		1680	100.0%	1.28 [1.22, 1.33]	•	
Total events	1381		1052					
Heterogeneity: Chi <sup>2</sup> =	64.82, df	= 17 (P	< 0.0000	01); l² =	74%			4
Test for overall effect:	Z=11.24	(P < 0.	00001)				Favours [Control] Favours [α-blocker	~
							ravous (control) i avous (a biocker	o1

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

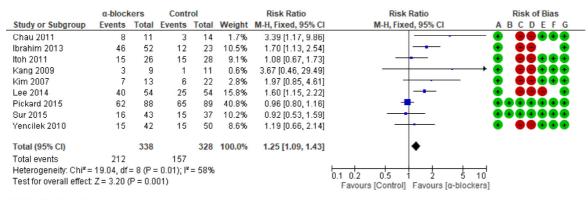
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

# d) Proximal Ureter 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)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias



There was statistical significance showing more rehospitalizations in the control group compared with the  $\alpha$ -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  $\alpha$ -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.<sup>73</sup> 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

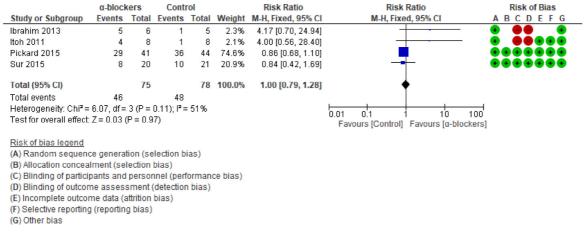


Fig. 3. Continued

extends from a negative number, there is a risk to do harm with treatment.<sup>73</sup> 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.<sup>6-14,20,37,63,65,71,72</sup>

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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -blockers with a control group. Pooled analysis would suggest that  $\alpha$ -blockers (and individual  $\alpha$ -blockers) do have a role in MET.

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Analysis of secondary outcome measures has demonstrated that use of  $\alpha$ -blockers led to a shorter time to expulsion of stones. Furthermore, the  $\alpha$ -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  $\alpha$ -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.<sup>74,79</sup> By the effect of  $\alpha$ -blockers relaxing ureter smooth muscles with the continual build-up of pressure above the stone, expulsion of the stone is more likely to occur.<sup>5,15-19,74-79</sup> 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  $\alpha$ -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.<sup>76</sup>

Although there were no major side effects that caused significant mortality or morbidity to any of the patients, the  $\alpha$ -blocker groups did have significantly more side effects. Of note, however, use of an  $\alpha$ -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

Study or Subgroup	a-block Events		Contr		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Risk of Bias ABCDEFG
Abdel-Meguid 2010	61	75	42	75	2.4%	1.45 [1.16, 1.82]		
Agrawal 2009	52	68	12	34	1.3%	2.17 [1.35, 3.48]		
hmad 2015	42	49	26	48	2.1%	1.58 [1.19, 2.10]		
Ahmed 2010	48	60	14	30	1.5%	1.71 [1.15, 2.56]		
N-Ansari 2010	41	50	28	46	2.2%	1.35 [1.03, 1.76]		
Ndemir 2011	25	31	11	29	1.2%	2.13 [1.29, 3.49]		
Nizadeh 2014	41	50	30	46	2.3%	1.26 [0.98, 1.61]	-	
Autorino 2005	28	32	19	32	1.9%	1.47 [1.08, 2.02]		
3ajwa 2013	23	30	11	30	1.2%	2.09 [1.26, 3.48]		
3alci 2014	19	25	9	25	1.0%	2.11 [1.20, 3.72]		
Cervenakov 2002	41	51	32	51	2.3%	1.28 [1.00, 1.65]	<u> </u>	
Chau 2011	19	22	14	20	1.9%	1.23 [0.89, 1.72]	T-	
De Sio 2006	45	50	27	46	2.2%	1.53 [1.18, 1.99]	-	
Dellabella 2003	30	30	21	30	2.3%	1.42 [1.12, 1.80]	_	• •••••
Dellabella 2005	68	70	45	70	2.7%	1.51 [1.26, 1.81]	-	
El-Gamal 2012	33	48	12	46	1.1%	2.64 [1.56, 4.44]		
ElSaid 2015	15	28	7	26	0.7%	1.99 [0.97, 4.09]		
Erturhan 2007	43	60	26	60	1.9%	1.65 [1.19, 2.30]		
Ferre 2009	27	35	24	37	2.0%	1.19 [0.88, 1.60]		
uryk 2015 Surbuz 2011	140 52	161 97	127 3	155 33	3.1%	1.06 [0.97, 1.17]		
Gurbuz 2011 Jan 2006	29	35	3 17	33	0.4% 1.7%	5.90 [1.97, 17.62]		
Hermanns 2009	39	30 45	40	45	2.8%	1.56 [1.09, 2.23] 0.97 [0.84, 1.14]	1	
brahim 2013	13	22	40	40	0.2%	2.36 [0.42, 13.37]		
toh 2011	40	55	31	56	2.1%	1.31 [0.99, 1.75]	-	<b>ě ě</b> ě e e ě
toh 2013	40	55	31	56	2.1%	1.31 [0.99, 1.75]	-	
(aneko 2010	24	31	17	34	1.6%	1.55 [1.05, 2.28]		
(ang 2009	6	10	7	10	0.8%	0.86 [0.45, 1.64]		
(eshvary 2006	18	20	11	24	1.3%	1.96 [1.24, 3.11]		ě ěěěěě
(im 2007	19	21	12	20	1.6%	1.51 [1.03, 2.21]		
Kirac 2013	25	42	19	39	1.5%	1.22 [0.81, 1.84]		
Kupeli 2004	8	15	3	15	0.3%	2.67 [0.87, 8.15]	<u> </u>	
.ee 2014	40	54	25	54	1.9%	1.60 [1.15, 2.22]		• ••• •
iatsikos 2007.	33	42	16	31	1.7%	1.52 [1.05, 2.22]		
ojanapiwat 2008.	27	50	1	25	0.1%	13.50 [1.95, 93.69]		- •••••
/lohseni 2006	29	32	20	32	2.1%	1.45 [1.08, 1.94]		
Aorua 2009	13	15	6	15	0.8%	2.17 [1.13, 4.15]		
/lustafa 2016	51	60	32	60	2.2%	1.59 [1.23, 2.07]	-	
Ochoa-Gomez 2011	22	32	23	33	1.9%	0.99 [0.71, 1.36]	+	
Pedro 2008	25	34	27	35	2.2%	0.95 [0.73, 1.25]	+	
Pickard 2015	216	249	202	246	3.1%	1.06 [0.98, 1.14]	t	
Porpiglia 2004	24	28	12	28	1.4%	2.00 [1.27, 3.15]		
Porpiglia 2006	18	30	8	24	0.9%	1.80 [0.95, 3.40]		
Porpiglia 2009	37	46	22	45	1.9%	1.65 [1.18, 2.29]	-	• • • • • • •
Rahim 2012	37	45	22	45	1.9%	1.68 [1.21, 2.34]		
Resim 2005	26	30	22	30	2.2%	1.18 [0.91, 1.53]		
Sameer 2014	30 40	35 45	7 23	35 45	0.8%	4.29 [2.18, 8.43]		
Sayed 2008 Sur 2015	40 36	45 52	23	45 59	2.0%	1.74 [1.28, 2.36] 1.51 [1.09, 2.11]		
/incendeau 2010	30 47	52 61	43	59 61	1.9% 2.5%	1.09 [0.88, 1.35]		
Vang 2008	47 51	64	43	31	1.8%	1.45 [1.03, 2.05]		
Vang 2008 Vang 2016	48	62	33	61	2.2%	1.43 [1.03, 2.05]		
/e 2017	40 1419	1642		1654	3.2%	1.10 [1.07, 1.13]		
encilek 2010	1415	42	1500	50	1.0%	1.19 [0.66, 2.14]		
ilmaz 2005	67	86	15	28	1.7%	1.45 [1.01, 2.09]		
/uksel 2015	32	35	25	35	2.4%	1.28 [1.01, 1.62]	<u> </u>	
Zehri2010	23	33	12	32	1.2%	1.86 [1.13, 3.07]		
Zhou 2011	48	88	13	43	1.2%	1.80 [1.10, 2.95]		
Fotal (95% CI)	_	4465		4141	100.0%	1.44 [1.34, 1.54]	,	
Total events	3608		2697					1
Heterogeneity: Tau² = I			•	r (P < I	J.00001);	r= 76%	0.01 0.1 1 10 1	00
Fest for overall effect: 2	2 = 10.32	(P < U.O	0001)				Favours [Control] Favours [ a-block	ers]
lisk of bias legend								
isk of bias legend A) Random sequence	e generati	on (sel	ection bis	is)				

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias) (G) Other bias

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.<sup>4,5,15-19</sup> These studies addressed use of  $\alpha$ -blockers in general and determined that they do have a role in MET to facilitate stone passage.<sup>4,5,16,17,19</sup> Two reviews found that the use of indivisible  $\alpha$ -blockers, alfuzosin or silodosin, is also effective

# g) Side Effects per patients

-

	a-block	(ers	Cont	rol		Risk Ratio	Risk	Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% CI	ABCDEFG
Abdel-Meguid 2010	5	75	0	75	0.4%	11.00 [0.62, 195.48]	-	•	- • •••••
Ahmed 2010	3	60	0	30	0.6%	3.56 [0.19, 66.72]	I —	-	
Al-Ansari 2010	9	50	5	46	4.4%	1.66 [0.60, 4.58]	1 -	•	
Autorino 2005	2	32	2	32	1.7%	1.00 [0.15, 6.67]	I		• •••••
Bajwa 2013	3	30	0	30	0.4%	7.00 [0.38, 129.93]	I —		• •••••
Balci 2014	2	25	1	25	0.8%	2.00 [0.19, 20.67]	I —	-	• •••••
Chau 2011	2	33	0	34	0.4%	5.15 [0.26, 103.33]	I —	<u> </u>	• ••••
De Sio 2006	3	50	2	46	1.8%	1.38 [0.24, 7.89]	ı —	·	• •••••
ElSaid 2015	7	28	0	26	0.4%	13.97 [0.84, 232.97]			- • ••••
Georgescu 2015	9	100	0	50	0.6%	9.59 [0.57, 161.57]	1 -	· · ·	$\bullet \bullet$
Hermanns 2009	4	45	1	45	0.8%	4.00 [0.47, 34.41]	1 -	· ·	
lbrahim 2013	11	80	0	32	0.6%	9.37 [0.57, 154.45]		· · · · ·	• •• •
Itoh 2011	6	89	0	92	0.4%	13.43 [0.77, 234.99]	1 +	· · ·	- • ••••
Itoh 2013	1	55	0	56	0.4%	3.05 [0.13, 73.38]	I —	· · · · ·	• •••••
Kupeli 2004	1	15	0	15	0.4%	3.00 [0.13, 68.26]	I —		• ••••
Mohseni 2006	3	32	0	32	0.4%	7.00 [0.38, 130.26]	I —		• ••••
Morua 2009	1	15	0	15	0.4%	3.00 [0.13, 68.26]	I —		• ••••
Mustafa 2016	8	60	10	60	8.4%	0.80 [0.34, 1.89]		_	
Ochoa-Gomez 2011	4	32	0	33	0.4%	9.27 [0.52, 165.55]	-		
Pedro 2008	12	32	0	35	0.4%	27.27 [1.68, 442.68]	]		+ ••••••••
Pickard 2015	0	378	1	379	1.3%	0.33 [0.01, 8.18]			
Porpiglia 2004	4	28	0	28	0.4%	9.00 [0.51, 159.70]	ı —	· · ·	
Porpiglia 2006	2	30	0	24	0.5%	4.03 [0.20, 80.21]	I —	· · · · ·	
Sameer 2014	3	35	0	35	0.4%	7.00 [0.37, 130.69]	ı —		
Wang 2008	6	64	0	31	0.6%	6.40 [0.37, 110.10]	I —	· · · · ·	
Wang 2016	10	62	2	61	1.7%	4.92 [1.12, 21.53]			
Ye 2017	92	1642	84	1654	70.5%	1.10 [0.83, 1.47]			
Yuksel 2015	6	35	0	35	0.4%	13.00 [0.76, 222.31]	-	•	
				_					
Total (95% CI)		3212		3056	100.0%	1.83 [1.47, 2.28]		•	
Total events	219		108						
Heterogeneity: Chi <sup>2</sup> = 3				²= 32%				10 20	+ 10
Test for overall effect: .	Z = 5.41 (F	° < 0.00	0001)				Favours [a-blockers]		

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

# h) Re-Hospitalisation rates

	a-block	ers	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG
Ahmad 2015	0	49	1	48	1.0%	0.33 [0.01, 7.83]		
Ahmed 2010	3	59	4	28	3.6%	0.36 [0.09, 1.48]		
Autorino 2005	3	32	7	32	4.6%	0.43 [0.12, 1.51]		• •••••
De Sio 2006	5	50	11	46	7.5%	0.42 [0.16, 1.11]		
Dellabella 2003	0	30	3	30	2.3%	0.14 [0.01, 2.65]		
Dellabella 2005	0	70	11	70	7.6%	0.04 [0.00, 0.72]	<b>-</b>	
ElSaid 2015	0	28	3	26	2.4%	0.13 [0.01, 2.46]		
Erturhan 2007	1	30	2	30	1.3%	0.50 [0.05, 5.22]		
Furyk 2015	20	198	23	195	15.2%	0.86 [0.49, 1.51]		
Georgescu 2015	3	100	7	50	6.1%	0.21 [0.06, 0.79]		••
Hermanns 2009	6	45	2	45	1.3%	3.00 [0.64, 14.08]	+	
Sameer 2014	5	35	27	35	17.8%	0.19 [0.08, 0.43]		
Vincendeau 2010	4	61	6	61	3.9%	0.67 [0.20, 2.25]		
Wang 2016	0	62	0	61		Not estimable		
Yencilek 2010	14	42	20	50	12.0%	0.83 [0.48, 1.44]		
Zehri2010	1	33	20	32	13.4%	0.05 [0.01, 0.34]	<b>_</b>	
Total (95% CI)		924		839	100.0%	0.43 [0.33, 0.56]	•	
Total events	65		147					
Heterogeneity: Chi <sup>2</sup> =	31.49, df:	= 14 (P	= 0.005)	; <b>I</b> ² = 58	6%			7
Test for overall effect:			,				0.001 0.1 1 10 100 Favours [α-blockers] Favours [Control]	U

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Fig. 3. Continued

in increasing stone passage.<sup>15,18</sup> Our review mirrors previous reviews in that we have also confirmed the importance of  $\alpha$ -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.<sup>4,5,16-19</sup> 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.<sup>4,80</sup> Lastly, even the Cochrane review published had areas for improvement.<sup>17</sup> 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  $\alpha$ -blocker to a control group. Furthermore, we have calculated an NNT figure to best aid clinicians understand the benefit in the use of  $\alpha$ -blockers or lack of it for each category. This review has also analyzed individual  $\alpha$ -blocker results to get a better understanding of the individual  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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 posttreated stones, for example, benefits of  $\alpha$ -blockers post-ESWL.

# CONCLUSION

Pooled analysis of RCTs would suggest that  $\alpha$ -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.