Medical therapy to facilitate urinary stone passage: a meta-analysis

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Summary

Background Medical therapies to ease urinary-stone passage have been reported, but are not generally used. If effective, such therapies would increase the options for treatment of urinary stones. To assess efficacy, we sought to identify and summarise all randomised controlled trials in which calcium-channel blockers or α blockers were used to treat urinary stone disease.

Methods We searched MEDLINE, Pre-MEDLINE, CINAHL, and EMBASE, as well as scientific meeting abstracts, up to July, 2005. All randomised controlled trials in which calcium-channel blockers or α blockers were used to treat ureteral stones were eligible for inclusion in our analysis. Data from nine trials (number of patients=693) were pooled. The main outcome was the proportion of patients who passed stones. We calculated the summary estimate of effect associated with medical therapy use using random-effects and fixed-effects models.

Findings Patients given calcium-channel blockers or α blockers had a 65% (absolute risk reduction=0·31 95% CI 0·25–0·38) greater likelihood of stone passage than those not given such treatment (pooled risk ratio 1·65; 95% CI 1·45–1·88). The pooled risk ratio for α blockers was 1·54 (1·29–1·85) and for calcium-channel blockers with steroids was 1·90 (1·51–2·40). The proportion of heterogeneity not explained by chance alone was 28%. The number needed to treat was 4.

Interpretation Although a high-quality randomised trial is necessary to confirm its efficacy, our findings suggest that medical therapy is an option for facilitation of urinary-stone passage for patients amenable to conservative management, potentially obviating the need for surgery.

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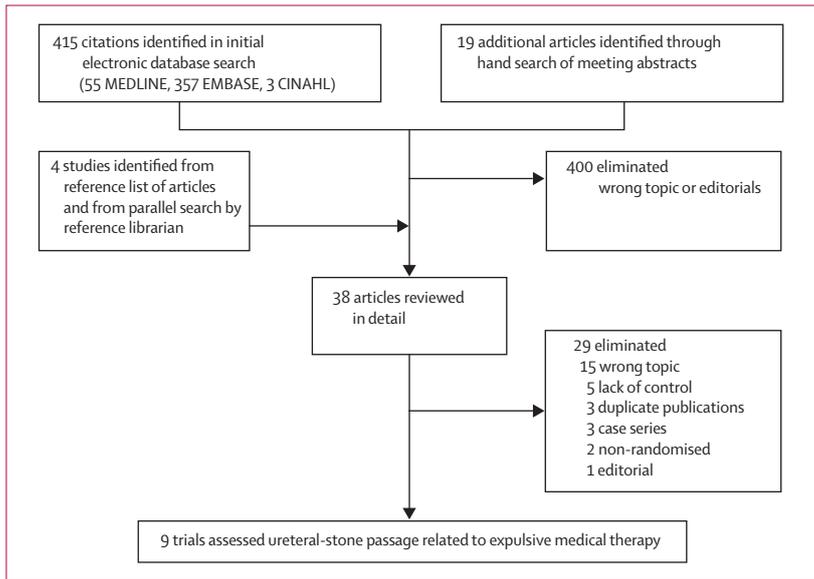MI 48109-0330, USA
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Introduction

The lifetime risk of urinary stone disease (urolithiasis) is estimated to be between 5% and 12% in Europe and the USA,[1–4] afflicting 13% of men and 7% of women.[5] Since 50% of patients will have a recurrence of renal colic within 5 years of their first episode,[6] urolithiasis is a chronic disease with substantial economic consequences and great public health importance. In the USA alone, nearly 2 million outpatient visits were needed for the disease in 2000, with expenditures for inpatient and outpatient claims totalling US$2·1 billion.[7]

Although patients with urolithiasis might be asymptomatic, many have pain and thus commonly present to emergency or outpatient departments. Provided that these patients do not need renal pelvic decompression—ie, they do not have a solitary kidney or obstructing pyelonephritis—and that pain relief can be obtained, a trial of conservative non-surgical therapy is warranted, since many of these stones pass spontaneously. Indeed, studies have shown spontaneous passage rates of 71%–98% for small (≤5 mm) distal ureteral stones,[8–10] with urinary-stone size and location being the two most important predictors of stone passage.[9] In view of this relation, investigators have sought ways of assisting the process with the use of drugs, thereby reducing the need for surgical intervention.

Use of calcium-channel blockers and adrenergic α-antagonists for expulsive medical therapy has been proposed as a way to enhance stone passage. Interest in these drug classes stems from our understanding of ureteral smooth-muscle physiology and urinary obstruction.[11–17] Despite growing evidence from clinical trials in support of its efficacy, expulsive therapy is rarely used. Two explanations for underuse are: first, that minimally invasive surgical techniques, such as shock-wave lithotripsy and ureteroscopy have evolved to allow for resolution of stone burden,[18,19] but carry measurable risks and are costly;[18,20–27] and second, that reports of empirical data for medical therapies have appeared only in urological publications, and therefore, the availability of such therapies might not be well known to physicians from other disciplines. Since many specialists—such as emergency-department physicians, internists, and family practitioners—serve as the initial conduit into the health-care system for patients with urolithiasis, a knowledge gap might exist. Therefore, we obtained data from clinical trials to derive a quantitative estimate of ureteral-stone expulsion associated with medical therapy.

Methods

Eligibility criteria

We used guidelines from the Quality of Reporting of Meta-Analyses conference.[28] Inclusion criteria were established before the search. Randomised controlled trials of urolithiasis in any language were eligible. Only those studies in which a calcium-channel blocker or an adrenergic α-antagonist was used as the main therapy

Figure 1: Study selection process

antispasmolytics, anticholinergic therapy, or corticosteroids. In the instance of many publications from a single institution or group, we contacted the primary investigator to determine whether these reports were generated from the same study population. Results from duplicate populations were excluded. We specified a minimum follow-up period of one week to allow for spontaneous stone passage.

Search strategy

English and non-English language publications were searched for human studies relating to expulsive medical therapy from Jan 1, 1981, to July 31, 2005. We did an electronic search of MEDLINE, Pre-MEDLINE, CINAHL, and EMBASE. We searched by exploding and combining the following medical subject heading terms: "calcium channel blocking agent" with "urolithiasis" and "alpha adrenergic receptor blocking agent" with "urolithiasis". A research librarian at the University of Michigan Medical School did an independent search to confirm the exhaustiveness of our search.

In an effort to identify further reports, we hand searched abstracts from the annual meetings of the World Congress of Endourology, the European Association of Urology, and the American Urological Association between 1999 and 2005. We corresponded with the first or senior authors of the published trials and conference abstracts that met our inclusion criteria to clarify questions about

for ureteral-stone disease were included; therefore, we excluded trials in which medical therapy was examined as an adjuvant to surgery. For the purpose of ascertaining trial eligibility, control groups were defined a priori as those not having received any additional medical therapy to ease urinary-stone passage—eg, other vasodilators,

Study	Year	Location	Number randomised	Number completed	Mean age (years, SD)*	% female*	Mean stone size (mm, SD)*
Cooper[40]	2000	Grand Rapids, MI, USA	Total 76	Treatment 35 Control 35	For patients who completed the study: Treatment 45·4 Control 46·4	For those who completed the study: Treatment 17% Control 34%	For those who completed the study: Treatment 3·86 Control 3·91
Porpiglia[42]	2000	Turin, Italy	Treatment 48 Control 48	Treatment 46 Control 46	Treatment 44 Control 49	Treatment 46% Control 50%	Treatment 5·8 (1·8) Control 5·5 (1·4)
Skrekas[45]	2003	Athens, Greece	Treatment 46 Control 46	Treatment 46 Control 46	Median age: Treatment 43·0 Control 41·8	Treatment 41% Control 46%	Treatment 5·0 Control 5·5
Porpiglia[43]	2004	Turin, Italy	Treatment 1 30 Treatment 2 28 Control 28	Treatment 1 29 Treatment 2 27 Control 28	Treatment 1 45·6 (12) Treatment 2 50·5 (17) Control 42·7 (16)	Treatment 1 37% Treatment 2 36% Control 43%	Treatment 1 4·70 (1·47) Treatment 2 5·42 (1·54) Control 5·35 (1·49)
Küpeli[41]	2004	Ankara, Turkey	Treatment 15 Control 15	Treatment 15 Control 15	Treatment 41·90 Control 43·74	n/a	Treatment 4·7 Control 4·9
Tekin[53]	2004	Istanbul, Turkey	Treatment 36 Control 39	Treatment 36 Control 39	Treatment 44 Control 42	n/a	Treatment 7·3 Control 6·8
Taghavi[52]	2005	Mashhad, Iran	Treatment 1 20 Treatment 2 20 Control 24	Treatment 1 20 Treatment 2 20 Control 24	Overall 38	Overall 45%	n/a
Yilmaz[46]	2005	Kirkale, Turkey	Treatment 1 29 Treatment 2 28 Treatment 3 29 Control 28	Treatment 1 29 Treatment 2 28 Treatment 3 29 Control 28	Treatment 1 40·62 (10·27) Treatment 2 41·67 (11·41) Treatment 3 42·13 (10·46) Control 41·60 (12·01)	Treatment 1 69% Treatment 2 68% Treatment 3 69% Control 32%	Treatment 1 6·00 (1·25) Treatment 2 5·96 (0·83) Treatment 3 5·93 (0·88) Control 6·07 (1·41)
Resim[44]	2005	Kahramanmaras, Turkey	Treatment 30 Control 30	Treatment 30 Control 30	Treatment 35·3 (10·9) Control 33·5 (9·7)	Treatment 27% Control 23%	Treatment 7·8 (2·3) Control 7·8 (2·2)

Data are number (SD) unless otherwise indicated. All studies took place in outpatient settings. n/a=data not available. *Values are for the starting population unless indicated otherwise.

Table 1: Study and patient summary characteristics

their studies, and to find out about unpublished or continuing studies. We also contacted major drug manufacturers to inquire about unpublished industry-sponsored trials.

Data reviews and statistical analysis

Two reviewers independently extracted data from every study using a standardised form. To reduce bias, one of the reviewers was blinded to the source of the publication and to the authors' names. Inconsistencies between reviewers' data were resolved through discussion until a consensus was reached. We were able to contact investigators from five of the studies for which we needed clarification. Three of the four drug companies with which we corresponded replied to our inquiries.

We wanted our findings to be generalisable to all adults with ureteral stones amenable to a trial of conservative management. The primary endpoint in the studies was the proportion of patients who passed stones (cumulative incidence). Therefore, we summarised effect size using a pooled risk ratio with 95% CIs, comparing the proportion of patients taking medical therapy who passed stones with the proportion of those not taking medical therapy (controls) who passed stones. We used both Mantel-Haenszel fixed-effects and DerSimonian and Laird random-effects models to produce across-study risk ratios. Since both models yielded similar results, the Mantel-Haenszel fixed-effects model only is reported here. Except where indicated otherwise, we did our analysis on an intention-to-treat basis with the assumption that dropouts failed to pass their stones. To assess heterogeneity, we used Cochran's Q-test of heterogeneity (which follows a χ^2 distribution) and the I^2 statistic (which measures the proportion of inconsistency in individual studies that cannot be explained by chance).[29] On the basis of the pooled risk ratio and the baseline risk, we calculated the number needed to treat (NNT). The 95% CIs for numbers needed to treat were calculated with the Newcombe-Wilson hybrid score method.[30]

To assess the effect of individual studies on the summary estimate of effect, we did an influence analysis, in which the pooled estimates were recalculated omitting one study at a time. We assessed publication bias using Rosenthal's fail-safe number—ie, the number of non-significant, unpublished studies that would be needed to reduce a statistically significant observed result to non-significance at $\alpha=0.05$).[31] We also calculated the more recently described Rosenberg fail-safe number,[32] which is weighted by study variance and, therefore, might be more appropriate to meta-analyses that combine weighted effect sizes. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n +10, when n is the number of studies included in the meta-analysis.

Since there is no gold standard for assessment of the validity of randomised controlled trials, we addressed quality on the basis of every study's conformity with the criteria suggested by the Cochrane Collaboration[33]—ie, method of randomisation, conceal-ment of allocation, blinding, loss to follow-up, and intention-to-treat analysis. We then did sensitivity analyses based on the criteria for which there was variation from the Cochrane criteria.

Subgroup analyses by drug type were done on the basis of a priori decisions and included an assessment of tamsulosin alone, nifedipine alone, all adrenergic α antagonists, and the combined use of nifedipine and corticosteroids. Studies that used chemically different drugs with similar mechanisms of action (such as tamsulosin and terazosin) or different formulations of the same drug (such as nifedipine immediate-release versus sustained-release) were grouped together for analysis.

Stata version 9.0 (Stata Corp, College Station, Texas) was used for all calculations.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

415 studies were identified in the electronic database search (figure 1). The review of meeting abstracts yielded 19 additional studies. We excluded from detailed review any articles that were either non-research reports, such
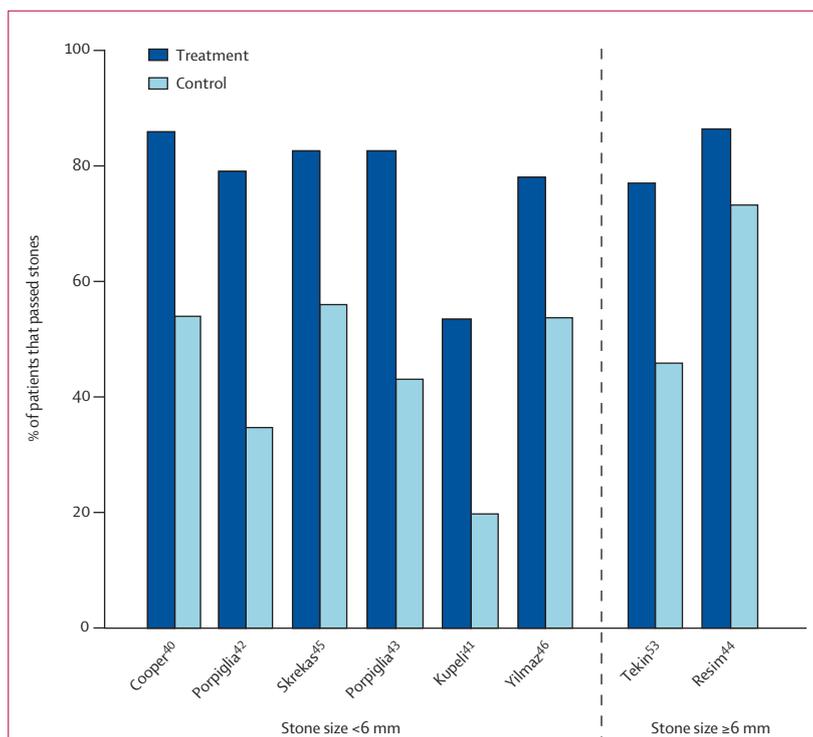

Figure 2: Percentage of patients who passed stones stratified by study group and mean stone size

	Treatment group event rate*	Number needed to treat*	95% CI*
Control group event rate			
10·0%	16·5%	16	8·7–75·4
20·0%	33·0%	8	5·1–15·7
30·0%	49·5%	5	3·8–8·2
40·0%	66·1%	4	3·0–5·3
50·0%	82·6%	3	2·5–3·9
60·0%	99·1%	3	2·2–3·0

*Based on relative risk=1·65 applied to the control group event rates.

Table 2: Number needed to treat for various background proportions of spontaneous stone passage

as editorials or commentaries, or studies on the wrong topic—eg, trials that used different interventions, trials with different outcomes measured, or observational studies.

There were five additional randomised studies that made a substantial contribution to the literature, including the first trial of expulsive medical therapy.[34–38] These studies were excluded from the final meta-analysis because none of them had a true control group. Specifically, Borghi and colleagues[34] randomly assigned patients nifedipine and corticosteroids versus corticosteroids alone. Dellabella and co-workers[36,37] did two studies examining the efficacy of medical therapy. In their first,[36] patients with urolithiasis were randomly assigned tamsulosin and corticosteroids versus corticosteroids alone. 2 years later, in their second study,[37] patients were randomly assigned tamsulosin or nifedipine and corticosteroids versus corticosteroids alone. Additionally, the control groups in

See **Online** for webtable 1
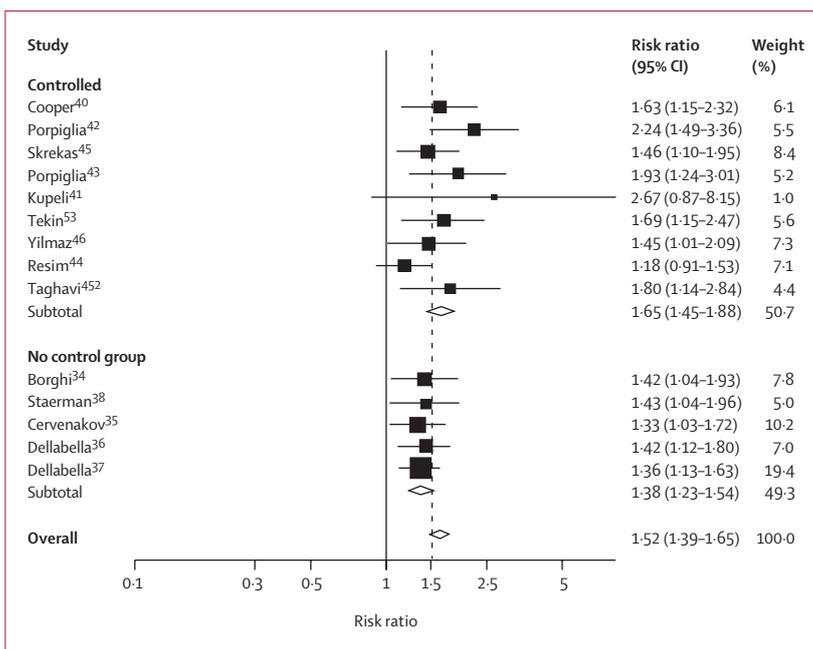
both of these studies also received treatment with the antispasmolytic phloroglunicol or its trimethoxy-benzene derivative. Similarly, Staerman and colleagues[38] randomly assigned patients nifedipine versus phloroglucinol.

Červenàkov and colleagues randomly assigned patients standard therapy (including the antispasmolytic, diazepam) versus standard therapy and tamsulosin.[35] Because of the anti-inflammatory effect of corticosteroids and the smooth-muscle relaxation activity of antispasmolytics, the control groups of these trials were given potentially active therapies that might have promoted ureteral-stone passage. For this reason, they were not eligible for inclusion in our main analysis. Indeed, corticosteroids have been shown to increase stone passage rates.[39] Although these studies did not meet the strict inclusion criteria, we did a separate sensitivity analysis in which their data were used to examine the effect of their inclusion on the overall risk ratio.

In seven of the studies pooled, both treatment and control groups received scheduled or on-demand doses of non-steroidal anti-inflammatory drugs (NSAIDs).[40–46] These drugs are highly effective in the symptomatic relief of acute renal colic.[47,48] Additionally, NSAIDs might augment urinary stone expulsion.[49,50] Yet the only randomised, double-blind, placebo-controlled trial to investigate the effect of NSAIDs on stone-passage rates showed no difference between NSAIDs and control.[51] None of the studies that we pooled were designed to examine the effect of NSAIDs on our primary outcome; however, we did a post-hoc subgroup analysis for the studies that included NSAIDs in both treatment and control groups, as well as for the two studies in which no NSAIDs were used.[52,53]

We then reviewed the remaining 38 articles in detail to determine if they met inclusion criteria. The final study population consisted of nine relevant trials that examined the use of calcium-channel blockers or α blockers to augment urinary-stone passage.[40–46,52,53]

693 patients were randomised into the nine trials included in the meta-analysis (table 1). All patients were treated on an outpatient basis. The mean age of participants ranged from 34·4 years to 46·5 years, and the percentage of women in the studies varied from 25% to 60%. Mean stone size ranged from 3·9 mm to 7·8 mm. In all but one study,[40] treated patients had stones located in the distal third of the ureter. There were 12 dropouts across all nine trials; seven patients from the intervention groups and five from the control groups.

The medical treatments and follow-up as well as the primary and secondary outcomes and recorded side-effects are shown in webtable 1. Treatment duration ranged from 7 days to 6 weeks, or until stone passage if before than 6 weeks. Follow-up varied from 15 days to 48 days. In some trials, several drugs were given to the treatment groups; for three studies, corticosteroids were given to the treatment groups in addition to the calcium-channel blocker nifedipine.[40,42,43] The treatment and control groups received NSAIDs in seven trials.[40–46]

Figure 3: Forest plot of risk ratios of stone passage, stratified by presence of control group
Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

The primary outcome of interest—the proportion of patients who passed their stones—occurred more often in the treatment groups than in the control groups in all nine studies. Figure 2 shows the percentage of patients who passed stones, stratified by study group and mean stone size for each of the studies. In six trials, information was available for the mean time to stone passage; mean time to passage ranged from 6 days in several treatment groups to 20 days in one control group.[40,42,43,45,46,52] In five of these six trials, the treatment group had shorter mean times to stone expulsion than the control group.

The fixed-effects Mantel-Haenszel pooled risk ratio was 1·65 (95% CI, 1·45–1·88), p<0·0001, indicating a 65% higher risk of stone passage associated with medical therapy. There was no significant heterogeneity in the studies pooled (χ^2 test, p=0·196). The I^2 statistic was 28%. The pooled risk difference was 0·31 (0·25–0·38). The number needed to treat was 4. When dropouts were excluded, the pooled risk ratio was 1·66 (1·46–1·88), p<0·0001. The baseline occurrence of stone passage in the control group, across all nine studies, was 0·47. Table 2 shows the effect of varying the background occurrence of spontaneous stone passage on the number needed to treat, which ranged from three patients (background occurrence=60%) to 16 patients (background occurrence=10%). The Rosenthal fail-safe number was calculated as 175 studies, and the Rosenberg fail-safe N was 105 additional non-significant studies necessary to reduce the pooled risk ratio to non-significance at α=0·05.

Figure 3 shows the study-specific risk ratios and the pooled estimate for the nine studies included, and for the five that did not have a true control. When these five studies were analysed with the previous nine, the overall risk ratio remained significant at 1·52 (1·39–1·65), p<0·0001. There was no significant heterogeneity with inclusion of these studies (χ^2=13·30, p=0·425). The I^2 statistic was 2·3%, which indicates that the variation in effect estimates is probably due to sampling error within trials rather than heterogeneity across trials.

The four studies in which treatment groups were given tamsulosin (without calcium-channel blockers) were pooled. This yielded a risk ratio of 1·52 (1·23–1·86), p<0·0001. When all studies in which an α blocker was used (n=5) were summarised, the pooled risk ratio was 1·54 (1·29–1·85), p<0·0001. In the two studies in which the intervention was nifedipine (without α blockers), the risk ratio was 1·51 (1·18–1·94), p=0·001. In three trials, the intervention was nifedipine with corticosteroids. When pooled, these studies resulted in a risk ratio of 1·90 (1·51–2·40), p<0·0001. None of the pooled risk ratios showed statistically significant heterogeneity across studies.

Although the effects of calcium-channel blockers and α blockers cannot be statistically isolated from those of the other medications used, we did a subgroup analysis

	Percentage of patients who passed their stones		Risk ratio (95% CI)
	Treatment	Control	
α blockers			
α blockers vs control			
Küpeli[41]	53% (8)	20% (3)	2·67 (0·87–8·15)
Tekin[53]	77% (28)	46% (18)	1·69 (1·15–2·47)
Yilmaz[46]	78% (67)	54% (15)	1·45 (1·01–2·09)
Resim[44]	87% (26)	73% (22)	1·18 (0·91–1·53)
Taghavi[52]	90% (18)	46% (11)	1·96 (1·24–3·11)
α blockers+steroids vs control			
Porpiglia[43]	85% (24)	43% (12)	2·00 (1·27–3·15)
α blockers+steroids vs steroids			
Dellabella[36]	100% (30)	70% (21)	1·43 (1·13–1·81)
Dellabella[37]*	97% (68)	64% (45)	1·51 (1·26–1·81)
α blockers+diazepam vs diazepam			
Červenàkov[35]†	80% (41)	60% (32)	1·33 (1·03–1·72)
Calcium-channel blockers			
Calcium-channel blockers vs control			
Skrekas[45]	83% (38)	56% (26)	1·46 (1·10–1·95)
Taghavi[52]	75% (15)	46% (11)	1·64 (0·99–2·71)
Staerman[38]‡	91% (21)	64% (16)	1·43 (1·04–1·96)
Calcium-channel blockers+steroids vs control			
Cooper[40]	82% (31)	50% (19)	1·63 (1·15–2·32)
Porpiglia[42]	79% (38)	35% (17)	2·24 (1·49–3·36)
Porpiglia[43]	80% (24)	43% (12)	1·87 (1·17–2·97)
Calcium-channel blockers+steroids vs steroids			
Borghi[34]	79% (34)	56% (24)	1·41 (1·04–1·93)
Dellabella[37]*	77% (54)	64% (45)	1·20 (0·97–1·49)
α blockers vs calcium-channel blockers			
	α blockers	Calcium-channel blockers	
Without steroids			
Taghavi[52]	90% (18)	75% (15)	1·20 (0·90–1·61)
With steroids in each group			
Porpiglia[43]	85% (24)	80% (24)	1·07 (0·85–1·35)
Dellabella[37]	97% (68)	77% (54)	1·26 (1·10–1·44)

Data are % (number) unless otherwise indicated. *Control groups also received phloroglucinol (or its trimethoxy benzene derivative). Both treatment and control groups received cotrimoxazole and diclofenac. †Treatment and control groups received a cocktail of medications including diazepam, tramadol, aesculus, and diclofenac. ‡Control group also received phloroglucinol. Both treatment and control groups received ketoprofene.

Table 3: Outcomes of the studies pooled and of the studies excluded for absence of a true control, stratified by treatment regimen

to pool the two studies in which neither treatment groups nor control group received NSAIDs.[52,53] The resulting risk ratio was 1·74 (1·29–2·33), p<0·0001. The pooled risk ratio for the seven studies in which NSAIDs were used in both treatment and control groups was 1·63 (1·41–1·88), p<0·0001.

In some studies, corticosteroids were used in the treatment group; in others, they were used in both treatment and control groups. Table 3 summarises the
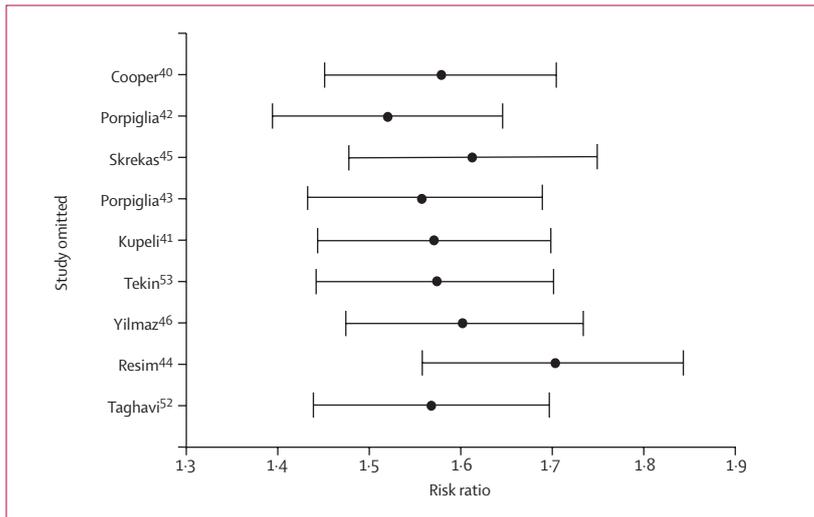
Figure 4: Influence analysis

results for the 14 randomised controlled trials listed in the forest plot (figure 3), with consideration of steroid use. When the studies of α blockers versus control[41,44,46,52,53] were compared with those of α blockers and corticosteroids versus control,[43] the incremental benefit of steroid use was small. A similar finding was noted for steroid use with calcium-channel blockers. There were three studies in which the effects of α blockers could be directly compared with that of calcium-channel blockers.[37,43,52] Two of these studies[43,52] reported no significant difference in stone expulsion for the two drug types, but one study[37] noted that α blockers were better than calcium-channel blockers (risk ratio 1·26; 1·10–1·44).

We did an influence analysis, in which the pooled estimates were recalculated omitting one study at a time. Figure 4 shows that the summary estimate of effect remained significant throughout this analysis. Resim and colleagues'[44] study had the largest effect on the overall estimate; with its omission, the overall risk ratio was 1·73 (1·50–1·99), p<0·0001.

Additionally, the three studies that included a description of the randomisation procedure (webtable 2) were analysed separately. The pooled risk ratio from this analysis was 2·14 (1·60–2·86), p<0·0001. We did a separate sensitivity analysis of the six studies for which there was no loss to follow-up (webtable 2). The pooled risk ratio from this analysis was 1·52 (1·30–1·77), p<0·0001. Finally, only those studies that were published as full manuscripts were pooled (webtable 2). The pooled risk ratio from this analysis was 1·68 (1·42–1·97), p<0·0001.

Three trials showed less need for analgesics in the treatment group than in the control group, as expressed by the mean amount of diclofenac used.[42,43,46] Two studies showed fewer episodes of acute pain in patients given expulsive therapy,[44,46] and one study showed that patients

given tamsulosin reported lower analogue pain scores.[44] Fewer days lost from work, fewer emergency department visits, and fewer surgical procedures in the treatment group than in the control group were reported in one trial.[40] Side-effects were not rigorously reported for all studies. However, the occurrence of therapy-related transient hypotension and palpitations was low at 3·3%–4·2%.[42,43]

Discussion
The pooled results of the randomised trials suggest that pharmacotherapy helps with passage of distal ureteral stones. Patients treated medically with calcium-channel blockers or α blockers had a 65% greater likelihood of spontaneous stone passage than did patients not given these drugs. This beneficial effect was consistent for both types of medical therapy. With the low risk-profile of these drugs and their wide therapeutic window, our results suggest that treating physicians should consider a new algorithm for the management of urolithiasis, in which treatment begins with a course of medical therapy, unless medically contraindicated.

Our findings are consistent with what is understood of ureteral pathophysiology associated with urinary-stone obstruction. In animal models, ureteral stones result in increased amplitude of ureteral smooth-muscle contraction, decreased frequency of contractions, and decreased ureteral pressure.[12] Evidence suggests that relaxing the ureter in the region of the stone and increasing hydrostatic pressure proximal to the stone help to facilitate ureteral stone passage.[17] Such relaxation can be accomplished by giving adrenergic α-antagonists and calcium-channel blockers,[13,15] the effects of which are mediated through the active calcium-channel pumps and adrenergic α-1 receptors present in ureteral smooth muscle.[11,14,16]

Additional benefits seem to be associated with expulsive medical therapy for urolithiasis. Several studies have reported that patients given such treatment have a significantly reduced time to stone passage,[42,43,45,46,52] significantly fewer pain episodes,[44,46] lower analogue pain scores,[44] and need significantly lower doses of analgesics.[42,43,46] With the caveat that side-effects were poorly categorised in these trials, calcium-channel blockers and α blockers seemed to be well tolerated, since there were only four patients across all studies who discontinued therapy.[42,43]

When medical therapy for urolithiasis is successful, surgical intervention is unnecessary. This advantage is important because the risks related to surgical intervention are not trivial.[23–25,27] Studies have reported overall complication rates after ureteroscopy of 10–20%, with major complications—eg, ureteral perforation, avulsion, and stricture—occurring in 3–5% of procedures.[21–23] Accumulation of perirenal fluid and subcapsular bleeds have been reported in 15–32% of patients treated with shock-wave lithotripsy.[20,27] This risk

is even more problematic since the re-treatment rate for shock-wave lithotripsy ranges from 4–50%.[18,54]

Furthermore, the potential cost savings of expulsive medical therapies in lieu of surgical interventions is large. In the USA alone, total annual expenditure for individuals with inpatient and outpatient claims for a primary diagnosis of urolithiasis increased by 50% between 1994 and 2000. Of the US$2·1 billion spent on this disease in 2000, $490 million were for emergency department services.[7] These numbers do not take into account the indirect costs, such as lost wages from missed work.

Surgical intervention for urolithiasis is costly, with reported estimates ranging from US$2645 for ureteroscopy to $4225 for shock-wave lithotripsy, with repeated therapy often needed.[18,26] Expulsive medical therapy, which relies mainly on generic drugs, is inexpensive. Based on drug-cost data obtained from the University of Michigan pharmacy, costs would range from US$10·74, for a 28-day course of doxazosin, to $104·41 for a 42-day course of tamsulosin, the only non-generic medication.

Our main meta-analysis is potentially limited by clinical (not statistical) heterogeneity, in view of the variation in the drugs given to the different treatment groups. To address this issue, we analysed drug classes separately. Both classes of drugs seemed to be beneficial, though the results suggested that there might be an additive effect when combined with corticosteroids. Further exploration of combined treatments might be useful.

Furthermore, our results might have been affected by publication bias, in which positive studies are more likely to be submitted and published than negative ones. Although the fail-safe numbers did not show evidence of publication bias, this potential drawback can only be adequately assessed through registration of prospective trials and not through retrospective review of published studies, as exists here.[55] We did specifically ask investigators and the drug companies about unpublished studies in our correspondence. All five investigators and one of the three drug companies that responded to our inquiry denied knowledge of unpublished data. Another limitation relates to the overall quality of the trials, eight of which were not blinded and six of which did not describe the randomisation procedures in detail. Additionally, most studies were done in Mediterranean countries, and it is unknown whether the treatment response would vary in patients from different settings.

A definitive high-quality randomised controlled trial is necessary to confirm the efficacy of calcium-channel blockers and α blockers in patients with urolithiasis. Since preliminary studies tend to overestimate treatment effects, we used the lower confidence limit of the pooled relative risk (1·45) and determined that a two-armed trial would need to include 226 patients (113 in each arm), in view of the background occurrence of stone passage of 0·47, with α=0·05 (two-sided) and power=0·90. If the

occurrence of stone passage in the controls is lower (30%), the sample size required would be 532; if the occurrence is higher (60%), the study would require 110 patients.

Thus the published evidence provides support for the use of expulsive medical therapy in the treatment of urolithiasis. Although minimally invasive procedures have evolved that allow for resolution of stone burden with less morbidity than traditional open surgery, these procedures expose patients to anaesthetic and surgical risks that might be unnecessary. Although a large confirmatory trial is advisable, our findings suggest that medical therapy might provide a viable alternative to surgery in patients with urolithiasis who are amenable to conservative management.

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