National Institute for Health and Care Excellence

Consultation

Renal and ureteric stones: assessment and management

Timing of surgery

NICE guideline

Intervention evidence review

July 2018

Consultation

This evidence review was developed by the National Guideline Centre

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Contents

1 Timing of surgery (early versus delayed intervention)

1.1 Review question: What is the most clinically and cost-effective length of time to manage people (adults, children and young people) with symptomatic or asymptomatic renal or ureteric stones conservatively before intervention (early versus delayed intervention)?

1.2 Introduction

The management of renal and ureteric stones is dependent on the site and size of the stone. It is known that stones in the ureter will pass spontaneously and the chance of this decreases with increasing size. The optimum length of time for “conservative“ treatment is not known and there is no clear consensus on the time scale.

Once the decision has been made to treat there is no clear consensus as to whether it is clinically and cost effective to treat with a primary intervention, shock wave lithotripsy (SWL) or ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL), or to relieve the patients’ symptoms of pain /obstruction with a JJ stent before definitive treatment. This option for management allows the patient to be treated by a planned elective procedure but results in an additional procedure, a time delay in treatment and possible complications and quality of life issues. There is a wide variation in management with both options in UK practice. There is uncertainty about whether treating the stone at the time of the initial presentation (if appropriate) is more effective and reduces resource use, than discharging and treating as an elective procedure at a later point in time.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People (adults, children and young people) with symptomatic and asymptomatic renal or ureteric stones
Intervention	Early surgical intervention (up to and including 48 hours) Only SWL, URS and PCNL will be considered.
Comparison	Delayed surgical intervention (after 48 hours) Only SWL, URS and PCNL will be considered.
Outcomes	Spontaneous stone passing Surgical intervention required
Study design	Randomised controlled trials (RCTs)

1.4 Clinical evidence

1.4.1 Included studies

Three studies were included in the review;[2, 4, 9] these are summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Heterogeneity

There was moderate heterogeneity between the studies when they were meta-analysed for the outcomes of stone-free state. Pre-specified subgroup analyses were unable to be performed due to a lack of reporting in the studies. A random effects meta-analysis was therefore applied to this outcome, and the evidence was downgraded for inconsistency in GRADE.

1.4.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Guercio 2011[2]	Intervention (n=141): immediate URS (within 12 hours) Comparison (n=130): delayed URS (median [range]: 20 [15-30] days) + medical treatment (pain management)	n=271 People with acute renal colic from ureteral stones Median stone size (range): 8 (5-18) mm Male to female ratio 163:81 Italy	Spontaneous stone passing Stone free rate (1 week): defined as the complete absence of residual fragments assessed with HUCT Surgical intervention (ancillary procedure: SWL) Surgical intervention (retreatment: second URS) Surgical intervention (stent insertion)	
Kumar 2010[4]	Intervention (n=80): immediate SWL performed within 48 hours of the onset of colicky pain Comparison (n=80): delayed SWL. SWL was performed after 48 hours of onset of colicky pain	n=160 People with a single radiopaque upper ureteral stone <1cm Mean stone size, mm (SD): delayed group 7.5 (1.7); immediate group 7.3 (1.5)	Stone free state (3 months): defined as no residual fragments, confirmed by radiography and ultrasonography Surgical intervention (retreatment) Surgical intervention (ancillary procedures)	

Study	Intervention and comparison	Population	Outcomes	Comments
	SWL was performed at a rate of 100Hz, and a maximum of 3000 shockwaves per session	Mean age, years (SD): delayed group 37.3 (2.5); immediate group 37.4 (2.08) Male to female ratio 1.28:1 India		
Uguz 2015[9]	Intervention (n=32): immediate SWL within 24 hours from referral. Comparison (n=31): delayed SWL within 3-7 days from referral. Patients received a NSAID and recommended oral hydration SWL performed in the supine position at a shockwave rate of 90 per minute, for a maximum of 3000-3500 pulses per session	n=63 People with radiopaque ureteric stones 5-20mm in size Mean stone size, mm (SD): delayed group 8.8 (2.87); immediate group 8.12 (3.16) Mean age, years (SD): delayed group 37.6 (12.8); immediate group 36.7 (12.7) Male to female ratio 3.8:1 Turkey	Stone free state (3 days): defined as no fragments or clinically insignificant fragments (<4mm), confirmed by NCCT Surgical intervention (retreatment) Surgical intervention (ancillary procedures)	

See appendix D for full evidence tables.

1.4.5 Quality assessment of clinical studies included in the evidence review

1.4.5.1 Adults, ureteric, <10mm

Table 3: Clinical evidence summary: Early versus delayed intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Delayed	Risk difference with Early (95% CI)
Spontaneous stone passing	271 (1 study) 20 days	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	Peto OR 0.12 (0.03 to 0.53)	Moderate	
				54 per 1000	47 fewer per 1000 (from 25 fewer to 52 fewer)
Stone free state	462 (3 studies)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, inconsistency	RR 1.09 (1.01 to 1.18)	Moderate	
				800 per 1000	72 more per 1000 (from 8 more to 144 more)
Ancillary procedures	465 (3 studies)	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.52 (0.32 to 0.84)	Moderate	
				194 per 1000	93 fewer per 1000 (from 31 fewer to 132 fewer)
Retreatment	465 (3 studies)	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.49 (0.3 to 0.81)	Moderate	
				263 per 1000	134 fewer per 1000 (from 50 fewer to 184 fewer)
Stent insertion	239 (1 study) 20 days	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.24 (0.17 to 0.35)	Moderate	
				800 per 1000	608 fewer per 1000 (from 520 fewer to 664 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because heterogeneity, I2=54%, p= > 0.1, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G. Unit costs

Table 4: UK costs of surgery

Procedure	Description	Cost	Source
Interventions			
Ureteroscopy	LB65C, LB65D and LB65E Major Endoscopic, Kidney or Ureter Procedures, 19 years and over. Elective schedule, weighted for complications and excess bed days LB65C, LB65D and LB65E Major Endoscopic, Kidney or Ureter Procedures, 19 years and over, Day case schedule, weighted for complications	£2,172 (50% elective and 50% day case)	NHS reference cost 2016-17
SWL (per session)	LB36Z Extracorporeal Lithotripsy Day case schedule	£452	NHS reference cost 2016-17
Stent removal			
Stent removal (a)	LB09D Intermediate Endoscopic Ureter Procedures, 19 years and over	£1,018	NHS reference cost 2016-17

Source: NHS reference costs[6]

(a) The stent would be inserted at the time of the URS (as this is the procedure it might follow rather than an SWL) so only the removal cost applies.

1.6 Resource costs

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

Early intervention is likely to lead to substantial savings from downstream resource use avoided such as stents. It is recognised that there will be investment needed in order to reconfigure the system to allow early intervention, but the cost of implementing SWL for example has been identified in the surgery recommendations, and is a relevant cost here, but not an additional cost of implementing this recommendation.

1.7 Evidence statements

1.7.1 Clinical evidence statements

Three studies compared early versus delayed intervention in the adult, ureteric <10mm population. All three studies reported the outcomes stone-free state, ancillary procedures and retreatment, and showed a clinically important benefit of early intervention (3 studies; n=462-465). One study reported the outcome spontaneous stone passing and showed a clinical benefit of delayed intervention (n=271), and one study reported stent insertion and showed a clinically important benefit of early intervention (n=239). The quality of evidence ranged from Moderate to Low quality. This was due to risk of bias, and imprecision. There was also inconsistency for the stone-free state outcome.

1.8 Recommendations

G1. Offer surgical treatment (see table 1) to adults with ureteric stones and renal colic within 48 hours of diagnosis or readmission, if:

- pain is ongoing and not tolerated, **or**
- the stone is unlikely to pass.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

Evidence showed a benefit of early intervention (within 48 hours) over delayed intervention (after 48 hours) in terms of stone removal, repeated or ancillary procedures and stent insertion. This could lead to substantial savings on a population level. The committee agreed that ureteric stones tend to be painful and if left untreated can lead to a loss of kidney function, so surgical treatment should be offered within 48 hours of diagnosis or readmission, to people presenting with a ureteric stones and renal colic, providing that ongoing pain is not tolerated or the stone is unlikely to pass. Although the evidence was from people with stones less than 20 mm, the committee agreed that stones of all sizes should be treated within this timeframe. There was no evidence for people with renal stones, and the committee considered that the timing of treatment for these stones should be prioritised according to the nature and severity of symptoms.

1.9.2 Impact of the recommendations on practice

This recommendation applies to people who present acutely with renal colic, and have ongoing pain that is not tolerated (following pain relief), or a stone that is unlikely to pass. This can be a first presentation a re-presentation because of ongoing pain. It only applies to people having primary treatment, rather than a secondary URS or second session of SWL. It is important to be clear that all patients with ureteric stones are likely to present acutely at some point with renal colic, however not all will be eligible for early URS/SWL. Some people may be managed sufficiently with pain relief, and/or have a stone that is considered likely to pass (and therefore are either managed conservatively or could be candidates for MET) and although a decision for intervention with URS/SWL might be made – these will be people in whom surgery will be planned for a later date. Hence the wording of the recommendation also covers those who re-present as someone may become eligible for surgery within 48 hours if they develop ongoing pain or there stone is now considered unlikely to pass. Current practice for this population is to aim to treat ureteric stones with an elective surgical procedure within 4 to 6 weeks, although practice can vary and is influenced by the availability of services. During this period, people are likely to have a stent inserted while waiting for surgery.

These recommendations are likely to result in a change in practice because services would need to be reconfigured to allocate more theatre time for emergency surgery. More equipment would also be needed for SWL, such as more responsive networks of mobile lithotripters, more fixed-site machines or better organised referral systems. It is recognised that investment will be needed to reconfigure the system to allow early intervention. As early intervention is likely to lead to substantial savings from downstream resource use avoided such as stents, this is likely to outweigh any implementation costs, and therefore this recommendation is not expected to have a cost impact.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The committee agreed that spontaneous stone passing and surgical intervention required were the critical outcomes for this review.

1.10.1.2 The quality of the evidence

The quality of the evidence in this review ranged from a GRADE rating of moderate to very low. This was due to presence of selection bias and outcome reporting bias, resulting in a high risk of bias rating. Additionally, the imprecise nature of the results extracted and analysed in this review further downgraded the quality of the evidence.

1.10.1.3 Benefits and harms

Evidence for adults, children and young people with both symptomatic and asymptomatic renal or ureteric stones was searched for; however no evidence was identified for children, those with asymptomatic stones, or renal stones. The committee therefore agreed that the recommendations should only apply to those with adults with symptomatic ureteric stones.

The committee noted that as expected, the number of people spontaneously passing a stone was higher in the delayed intervention group, however this was not clinically significant, and the number of people experiencing this outcome was small. There were fewer stents inserted (post-surgery), fewer ancillary procedures and fewer retreatments in the early intervention group. There were also more stone free people following early treatment compared to delayed treatment. The committee noted that there was evidence from one study regarding early versus delayed URS, and evidence from 2 studies where the participants received SWL.

The committee considered the evidence for URS and noted that spontaneous stone passage was low compared to what would be expected in clinical practice. They further noted that a bigger difference between stone passage at 12 hours and 3 weeks would be expected. The committee also noted that this evidence was based on a study where early treatment was defined as URS performed within 12 hours, and discussed that this generally would not be possible in current UK clinical practice.

In terms of SWL, the committee noted that early treatment was within 48 hours of onset and 24 hours of referral, which was also likely to be within 48 hours of onset. The committee noted that although this may still not reflect current UK practice, other than those large centres which have lithotripters, it would be achievable providing there was increased access to equipment.

The committee discussed that although the evidence was from a population with a mean stone size less than 10 mm, this did include a range of stone sizes up to 20 mm, which may have impacted the results, especially given the small study sizes. They discussed that even

within the less than 10 mm group there are differences in terms of the likelihood of stone passage and response to treatment with MET, for example a stone <4mm is more likely to pass spontaneously, whereas a stone of >7 mm is likely to require intervention.

Overall, the committee agreed that this evidence suggests that the earlier a stone is treated, the easier and more effective SWL is. They noted from clinical experience that this could be due to the position of the stone, as it may be earlier in its passage and therefore in the proximal ureter, and it is easier to localise proximal stones compared to distal stones. It may also be due to there being less swelling and inflammation around the stone, making the targeting of the stone easier and the shockwave more effective. They considered that this has important implications in terms of reducing the need for further treatment, and also in terms of patient quality of life. They noted that not everyone presenting with renal colic due to a ureteric stone would need surgical treatment within 48 hours. Only those who have ongoing pain that persists after analgesia and is not tolerated, or those who have a stone that is unlikely to pass spontaneously, should be offered urgent surgical treatment, due to concerns about prolonged pain, and potential damage to the kidney caused by the ureter being blocked.

1.10.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The interventions being compared are the same surgery at different time points. However, differences in cost could arise if some people pass their stone before the delayed intervention, and therefore some surgeries are avoided. On the other hand, there may be more complications from delaying surgery, in which case surgery could become more complicated and require more resource use.

The clinical review has shown that there were more stone free people in the early intervention group. This was more so with SWL than URS. The committee thought this was likely to be because of oedema from delay which makes the intervention more difficult. This would impact resource use from avoiding further treatment. There was also a clinically meaningful decrease in ancillary procedures, retreatment, and stents inserted in the early group. This would lead to savings and also a positive impact on quality of life from clearing a stone sooner, and avoiding disutility from having a stent. Currently, in practice some people (having URS) would have a stent inserted and have a planned procedure at a later date, hence why stents can be avoided from treating early. There was however no information on adverse events whilst the delayed group were waiting for their scheduled surgeries e.g. unplanned hospital admissions. Overall there was a benefit demonstrated of early intervention, and given the resource use avoided, quality of life benefit from more people being stone free, and the negative quality of life impact of stents – early intervention is likely to be a dominant strategy.

The committee opinion was that the evidence was strong enough to offer URS or SWL within 48 hours of diagnosis or readmission. However there were caveats to this as the populations in the studies were in secondary care who had presented acutely with renal colic. The committee discussed that everyone is likely to present acutely, however not all should have surgery within 48 hours, as some can be managed with pain relief, and also for others the clinician may feel the stone is likely to pass on its own (with either conservative management or MET (if indicated). Hence this recommendation is for those patients who have either ongoing pain that is not tolerated, or a stone which is unlikely to pass and as a result there are adverse event risks and concerns about potential kidney damage. The committee however did not want to caveat the recommendation with a particular stone size, as the studies in the review had a mean stone size of under 10mm, but the ranges were very large, therefore covering a broader population. It is also important to note that the population are also those having primary treatment, as those having failed a first treatment of URS would have a stent inserted. Also with regards to SWL, it is about the first session: as if services

allow a first session to be completed in a timely manner, then these services would also benefit the patient for any retreatments.

These recommendations are likely to result in a change in practice because services would need to be reconfigured to allow more ring-fenced theatre space for example, for emergency surgery. Additionally for SWL; more equipment would be needed such as more responsive networks of mobile lithotripters or more fixed site machines or better organised referral systems. This may also have staff implications such as more staff required to operate equipment. This is likely to have a resource impact, but is also dependent on a number of factors; SWL has been recommended as the first line of treatment for several groups in the surgery review, in which case implementation of more (or improved) access to SWL can benefit multiple recommendations in the guideline. Additionally, there are likely to be large savings from treatments and stents avoided. As an estimate; there are around 20,000 URS procedures per year (GC estimate but also similar to HES/NHS reference cost figures). Not all of those would be for ureteric stones, but the majority probably are. If around 75% of these presented acutely as emergencies and if, as based on the clinical review, there is a relative risk of 0.24 of stent insertion, then around £11 million could be saved from stents avoided alone. This would go some way towards investment needed for equipment/staff/running costs.

In summary, the overall resource impact is unclear and depends upon the balance of savings and investment required to implement the recommendation.

1.10.3 Other factors the committee took into account

The committee discussed that from a patient's perspective, although there may be a benefit of delayed intervention in terms of spontaneous stone passage, this may not outweigh the potential impact on quality of life due to living with periods of severe pain for several weeks.

The committee discussed usual practice when making decisions on whether to delay surgery. If a ureteric stone was 4mm or less then it would be usual to wait for up to 6 weeks for the stones to pass, however the addition of MET may increase the chance of spontaneous passage. The chance of spontaneous stone expulsion decreases with stone size and varies between patients. Stones between 4-7mm have less chance of passing spontaneously and MET may help, but a period of observation 2-4 weeks is normal clinical practice. Stones larger than 7mm have less chance of passing, even with the addition of MET, and therefore people with these size stones may undergo a primary intervention.

The committee considered that children and young adults may spontaneously pass larger stones, therefore it would be reasonable to have a period of observation or conservative treatment before intervention.The evidence was only in ureteric stones so the recommendation is not applicable to people with renal stones. However, the committee noted that ureteric stones are associated with a higher risk of adverse events and are likely to be more painful compared with renal stones. It is however acknowledged that clinicians should treat renal stones based on size and urgency as they would any individual with a stone in any location.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: timing of surgery (early versus delayed surgical intervention)

Field	Content
Review question	What is the most clinically and cost-effective length of time to manage people (adults, children and young people) with symptomatic or asymptomatic renal or ureteric stones conservatively before intervention (early versus delayed intervention)?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine whether early management of renal and ureteric stones leads to improved outcomes for patients.
Eligibility criteria – population / disease / condition / issue / domain	People (adults, children and young people) with symptomatic and asymptomatic renal or ureteric stones
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Early surgical intervention (up to and including 48 hours) Only SWL, URS and PCNL will be considered.
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Delayed surgical intervention (after 48 hours) Only SWL, URS and PCNL will be considered.
Outcomes and prioritisation	Critical outcomes: • Spontaneous stone passing • Surgical intervention required
Eligibility criteria – study design	Randomised controlled trials (RCTs). If no RCT evidence for children is available, cohort studies will be considered.
Other inclusion exclusion criteria	Exclude: • Bladder stones • Open surgery for renal (kidney and ureteric) stones • Non-English language studies

Proposed sensitivity / subgroup analysis, or meta-regression	Strata:
	• Population
	  ○ Adults (≥16 years)
	  ○ Children and young people (<16 years)
	• Stone size:
	  ○ <1 cm
	  ○ 1-2 cm
	  ○ >2 cm
	  ○ Staghorn
	• Stone site:
	  ○ Renal stone
	  ○ Ureteric stone

	Subgroups: • Pregnant women • Upper/lower ureteric stones
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10033
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual. Amended to be able to investigate whether treating the stone at the time of the initial presentation (if appropriate) is better than discharging and treating as an elective procedure. Defining early as 4 weeks was based on UK NHS practice, but did not address this question. The evidence that was found based on this was very limited and did not allow the committee to make recommendations. The committee were aware of other evidence that had been excluded because of these time definitions, and felt on reflection that the original protocol was too restrictive. GIRFT project has suggested that best practice is a primary URS performed at the patients' initial presentation.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox'

	developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Andrew Dickinson in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 6: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G *[in the Full guideline]*.

Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2014 NICE guidelines manual.[5] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:*

	• The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 14 March 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 14 March 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 3 of 12 CENTRAL to 2018 Issue 2 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/

11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Surgery/
28.	exp Surgical Procedures, Operative/
29.	surger*.ti,ab.
30.	((surgical or operative or chirurgic*) adj3 (therap* or treatment* or intervention* or procedure*)).ti,ab.
31.	((urologic* or ureter* or kidney or renal or invasive or non invasive or extracorporeal or extra corporeal or percutaneous or retrograde) adj3 (procedure* or operation* or techinique* or intervention*)).ti,ab.
32.	or/27-31
33.	Time Factors/
34.	Time to Treatment/
35.	((earl* or immediate* or first* or before or delay* or defer* or postpone* or belated or after* or wait* or time or timing) adj3 (surger* or therap* or treatment* or intervention* or procedure*)).ti,ab.
36.	(emergen* or acute).ti,ab.
37.	or/33-36
38.	32 and 37
39.	26 and 38
40.	randomized controlled trial.pt.
41.	controlled clinical trial.pt.
42.	randomi#ed.ti,ab.
43.	placebo.ab.
44.	randomly.ti,ab.
45.	Clinical Trials as topic.sh.
46.	trial.ti.
47.	or/40-46
48.	Meta-Analysis/
49.	exp Meta-Analysis as Topic/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.

52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	Epidemiologic studies/
60.	Observational study/
61.	exp Cohort studies/
62.	(cohort adj (study or studies or analys* or data)).ti,ab.
63.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
64.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
65.	Controlled Before-After Studies/
66.	Historically Controlled Study/
67.	Interrupted Time Series Analysis/
68.	(before adj2 after adj2 (study or studies or data)).ti,ab.
69.	or/59-68
70.	exp case control study/
71.	case control*.ti,ab.
72.	or/70-71
73.	69 or 72
74.	Cross-sectional studies/
75.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
76.	or/74-75
77.	69 or 76
78.	69 or 72 or 76
79.	39 and 47
80.	39 and 58
81.	79 or 80
82.	39 and 78
83.	82 not 81

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/

8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	surgery/
26.	surger*.ti,ab.
27.	((surgical or operative or chirurgic*) adj3 (therap* or treatment* or intervention* or procedure*)).ti,ab.
28.	((urologic* or ureter* or kidney or renal or invasive or non invasive or extracorporeal or extra corporeal or percutaneous or retrograde) adj3 (procedure* or operation* or techinique* or intervention*)).ti,ab.
29.	or/25-29
30.	time factor/
31.	time to treatment/
32.	((earl* or immediate* or first* or before or delay* or defer* or postpone* or belated or after* or wait* or time or timing) adj3 (surger* or therap* or treatment* or intervention* or procedure*)).ti,ab.
33.	(emergen* or acute).ti,ab.
34.	or/30-33
35.	30 and 34
36.	24 and 35
37.	random*.ti,ab.
38.	factorial*.ti,ab.
39.	(crossover* or cross over*).ti,ab.
40.	((doubl* or singl*) adj blind*).ti,ab.
41.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
42.	crossover procedure/
43.	single blind procedure/
44.	randomized controlled trial/
45.	double blind procedure/
46.	or/37-45
47.	systematic review/
48.	meta-analysis/

49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	Clinical study/
59.	Observational study/
60.	family study/
61.	longitudinal study/
62.	retrospective study/
63.	prospective study/
64.	cohort analysis/
65.	follow-up/
66.	cohort*.ti,ab.
67.	65 and 66
68.	(cohort adj (study or studies or analys* or data)).ti,ab.
69.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
70.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	(before adj2 after adj2 (study or studies or data)).ti,ab.
72.	or/58-64,68-71
73.	exp case control study/
74.	case control*.ti,ab.
75.	or/73-74
76.	72 or 75
77.	cross-sectional study/
78.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	or/77-78
80.	72 or 79
81.	72 or 75 or 79
82.	36 and 46
83.	36 and 57
84.	82 or 83
85.	36 and 81
86.	85 not 84

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s):ti,ab

#3.	((renal or kidney* or urinary or ureter* or urethra*) near/3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)):ti,ab
#4.	stone disease*:ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/3 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [General Surgery] explode all trees
#8.	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#9.	surger*:ti,ab
#10.	(surgical or operative or chirurgic*) near/3 (therap* or treatment* or intervention* or procedure*):ti,ab
#11.	(urologic* or ureter* or kidney or renal or invasive or non invasive or extracorporeal or extra corporeal or percutaneous or retrograde) near/3 (procedure* or operation* or techinique* or intervention*):ti,ab
#12.	(or #7-#11)
#13.	MeSH descriptor: [Time Factors] this term only
#14.	MeSH descriptor: [Time-to-Treatment] this term only
#15.	(earl* or immediate* or first* or before or delay* or defer* or postpone* or belated or after* or wait* or time or timing) near/3 (surger* or therap* or treatment* or intervention* or procedure*):ti,ab
#16.	(emergen* or acute):ti,ab
#17.	(or #13-#16)
#18.	#12 and #17
#19.	#6 and #18

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to renal and ureteric stones population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 9 March 2018	Exclusions Health economics studies
Embase	2014 – 9 March 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 9 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.

4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

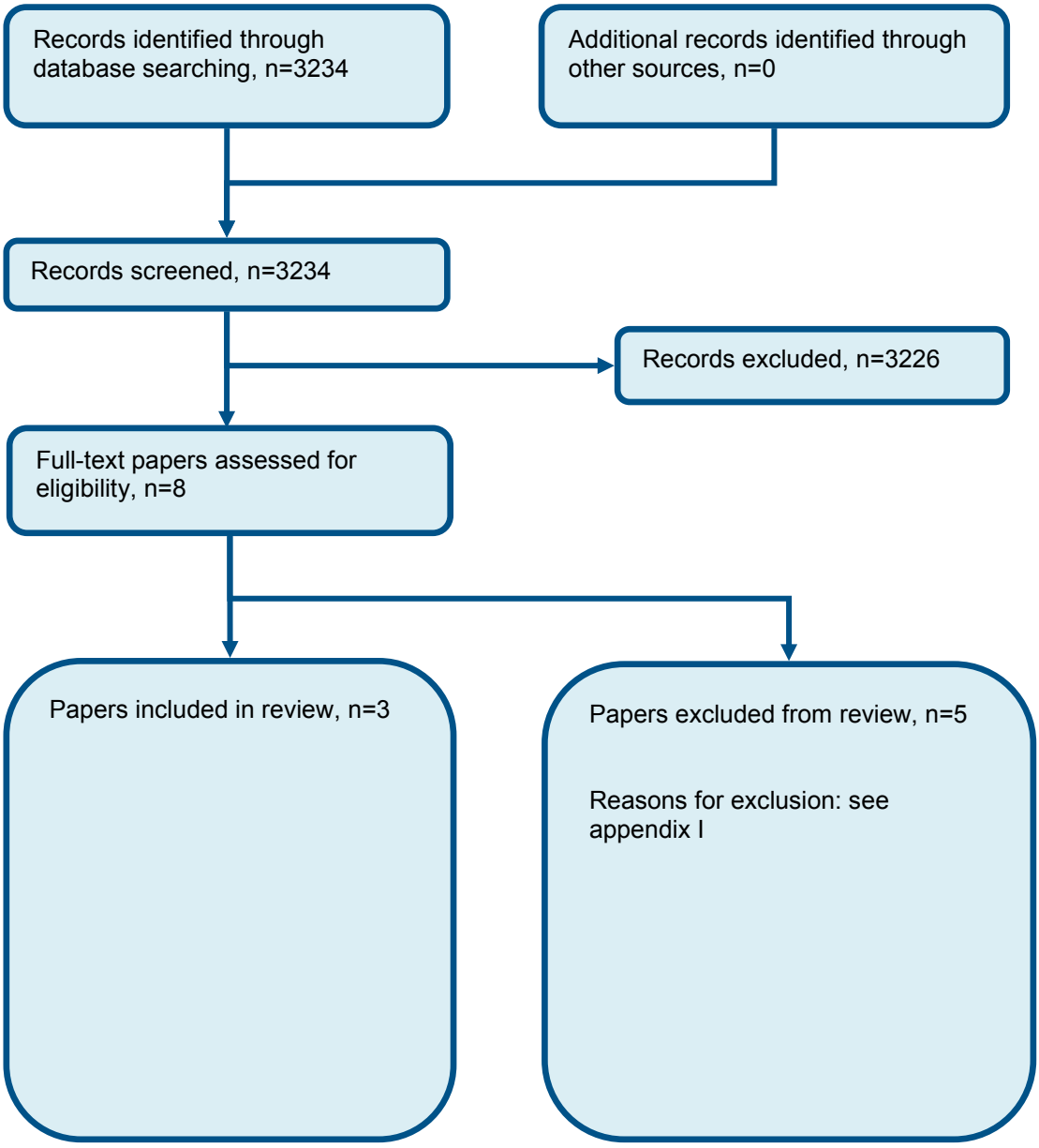
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR urolithiasis EXPLODE ALL TREES
#2.	(((nephrolitiasis or nephrolith or urolithiasis)))
#3.	((((renal or kidney or urinary or ureteric or ureteral or ureter or urethra*) adj2 (stone* or calculi or calculus or calculosis or lithiasis or colic))))
#4.	((stone disease*))
#5.	((((calculi or calculus) adj2 (stone* or lithiasis))))
#6.	(#1 OR #2 OR #3 OR #4 OR #5)

2
3

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of timing of surgery (early versus delayed intervention)



Appendix D: Clinical evidence tables

Study	Guercio 2011[2]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=271)
Countries and setting	Conducted in Italy; Setting: ED
Line of therapy	1st line
Duration of study	Intervention time: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults (≥16 years), ureteric stone <1 cm
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with acute flank pain caused by a ureteral stone (at least 5 mm) with hydronephosis
Exclusion criteria	Dilatation of the renal pelvis >30 mm or presence of a perirenal urinoma; initial renal function impairment; rectal temperature >38 C; blood leukocytes >20,000/dL; solitary kidney; history of ureteral stricture; severe vascular and/or metabolic pathology; intraoperative evidence of hydropyonephrosis.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): Early intervention: 51 (17-92); delayed intervention: 49 (20-82). Gender (M:F): 163/81. Ethnicity: Not stated
Further population details	1. Kidney pole: Not applicable 2. Neuropathic/ cerebral-palsy /immobility: Not applicable 3. Obesity /skin-to-stone distance: Not applicable 4. Pregnant women: Not applicable 5. Stone composition/hounsfield units: Not applicable 6. Uteric stone: Not applicable
Extra comments	An internal Double-J stent was inserted in case of significant tissue trauma and edema at the stone site or suspected ureteral perforation, in case of stones pushed back to the pyelocaliceal system, or failed ureteroscopy, where further interventions were needed.
Indirectness of population	No indirectness
Interventions	(n=141) Intervention 1: Ureteroscopy or RIRS - Semi-rigid or flexible. Ureteroscopy was performed under general or spinal anesthesia. A semi-rigid 6.5F ureteroscope and a flexible 7F ureteroscope were used.. Duration Immediate. Concurrent medication/care: Prophylactic IV antibiotics administered on induction of anesthesia. Indirectness: No indirectness

Study	Guercio 2011[2]
	(n=130) Intervention 2: Ureteroscopy or RIRS - Semi-rigid or flexible. Ureteroscopy was performed under general or spinal anesthesia. A semi-rigid 6.5F ureteroscope and a flexible 7F ureteroscope were used.. Duration Median 20 days (15 to 30 days). Concurrent medication/care: Prophylactic IV antibiotics administered on induction of anesthesia. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY VERSUS DELAYED INTERVENTION

Protocol outcome 1: Spontaneous stone passing
- Actual outcome for Adults (≥16 years): Spontaneous stone passing; Group 1: 0/141; Group 2: 7/130
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Stone free state
- Actual outcome for Adults (≥16 years): Stone free rate; Group 1: 130/139; Group 2: 90/100
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Ancillary procedure
- Actual outcome for Adults (≥16 years): Ancillary procedure (SWL); Group 1: 7/139; Group 2: 7/103
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Retreatment rate
- Actual outcome for Adults (≥16 years): Retreatment rate (second URS); Group 1: 2/139; Group 2: 3/103
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing::

Protocol outcome 5: Stent insertion
- Actual outcome for Adults (≥16 years): Stent insertion; Group 1: 27/139; Group 2: 80/100
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study	Guercio 2011[2]
Protocol outcomes not reported by the study	Surgical intervention required; Quality of life at Define; Hospitalisation at Define; Treatment success (stone free state, clinically insignificant residual fragments) at Define; New stone formation/incidence of stones/recurrence rate at Define; Use of healthcare services/retreatment rate at Define; Kidney function at Define; Recurrence rate at Define; Mortality at Define; Adverse events at Define; Pain intensity at Define; Length of stay at Define

Study	Kumar 2010[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in India; Setting: Hospital department
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Non-contrast CT and KUB
Stratum	Adults (≥16 years), ureteric stone <1 cm
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a single radiopaque upper ureteral stone <1cm, who presented with an episode of colicky pain
Exclusion criteria	Bleeding disorders, active urinary infection, age >60 years and <15 years, weight >100kg and <40kg, comorbid cardiovascular and respiratory illnesses, fever >38 degrees C, total leukocyte count >12000/dL, serum creatinine level >1.5mg/dL, solitary kidney, coexisting ureteral pathology including tumor/stricture, pregnancy and severe hydronephrosis
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Delayed group 37.3 (2.5); immediate group 37.4 (2.08). Gender (M:F): 46:34. Ethnicity: Not reported
Further population details	1. Kidney pole: Not applicable 2. Neuropathic/ cerebral-palsy /immobility: Not stated / Unclear 3. Obesity /skin-to-stone distance: Not stated / Unclear 4. Pregnant women: Non-pregnant 5. Stone composition/hounsfield units: Stone composition (Mixed). 6. Uteric stone: Upper ureteric stones
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Shock wave lithotripsy (SWL). SWL was performed within 48 hours of onset of colicky pain along with IV fluids and IM diclofenac. SWL was performed using the Dornier alpha-compact lithotripter at a shockwave rate of 100Hz. A maximum of 30000 shockwaves were delivered during each session. .

	Duration Not applicable. Concurrent medication/care: Patients initially received IV fluids and analgesics, which were repeated on demand if pain persisted (diclofenac 75mg IM q8h). Indirectness: No indirectness (n=80) Intervention 2: Shock wave lithotripsy (SWL). SWL was performed after 48 hours of onset of colicky pain along with IV fluids and IM diclofenac. SWL was performed using the Dornier alpha-compact lithotripter at a shockwave rate of 100Hz. A maximum of 30000 shockwaves were delivered during each session. . Duration Not applicable. Concurrent medication/care: Patients initially received IV fluids and analgesics, which were repeated on demand if pain persisted (diclofenac 75mg IM q8h). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IMMEDIATE SHOCK WAVE LITHOTRIPSY (SWL) versus DELAYED SHOCK WAVE LITHOTRIPSY (SWL)

Protocol outcome 1: Treatment success (stone free state, clinically insignificant residual fragments) at Define
- Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Stone free state at 3 months; Group 1: 69/80, Group 2: 64/80
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Use of healthcare services/retreatment rate at Define
- Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Retreatment rate at Not reported; Group 1: 11/80, Group 2: 21/80
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Ancillary procedure at Not reported; Group 1: 13/80, Group 2: 26/80
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; New stone formation/incidence of stones/recurrence rate at Define; Kidney function at Define; Recurrence rate at Define; Mortality at Define; Adverse events at Define; Pain intensity at Define; Length of stay at Define

Study	**Uguz 2012[9]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Turkey

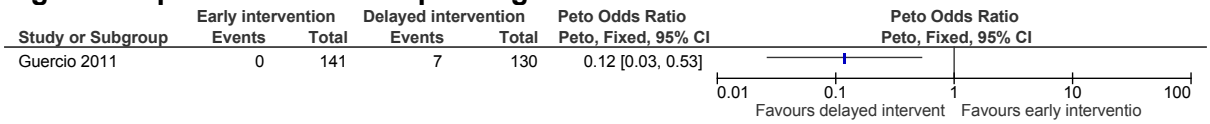
Study	Uguz 2012[9]
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Plain abdominal radiographs
Stratum	Adults (≥16 years), ureteric stone <1 cm
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with renal colic who had a radioopaque ureteric stone of 5-20mm
Exclusion criteria	Pregnancy, history of ureteral stenosis, ureteral tumor, open/endoscopic operations (URS, PNL), bleeding diathesis, severe cardiovascular and pulmonary disease, solitary kidneys, acute kidney failure (serum creatinine level greater than 1.5mg/dl), severe urinary tract infection or urosepsis, anticholinergic and alpha blocking agent use, age under 15 or above 80 years
Recruitment/selection of patients	Patients who applied to the emergency department
Age, gender and ethnicity	Age - Mean (SD): Delayed group 37.6 (12.8); immediate group 36.7 (12.7). Gender (M:F): 50:13. Ethnicity: Not reported
Further population details	1. Kidney pole: Not applicable 2. Neuropathic/ cerebral-palsy /immobility: Not stated / Unclear 3. Obesity /skin-to-stone distance: Not stated / Unclear 4. Pregnant women: Non-pregnant 5. Stone composition/hounsfield units: Not stated / Unclear 6. Uteric stone: Not stated / Unclear (Mixed: upper 65.05%, middle 9.55%, lower 25.3%).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Shock wave lithotripsy (SWL). SWL scheduled within 24 hours from referral. SWL was performed by the same urologist in all cases using a lithotripter with an electromagnetic generator with the patients in the supine position at a shock wave rate 90 per minute. Maximum pulses per session were 3000 for lower ureteric stones and 3500 for upper and middle ureteric stones. . Duration Not applicable. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=31) Intervention 2: Shock wave lithotripsy (SWL). SWL scheduled within 3-7 days from referral. SWL was performed by the same urologist in all cases using a lithotripter with an electromagnetic generator with the patients in the supine position at a shock wave rate 90 per minute. Maximum pulses per session were 3000 for lower ureteric stones and 3500 for upper and middle ureteric stones. . Duration Not applicable. Concurrent medication/care: Patients received a non-steroidal anti-inflammatory drug (diclofenac sodium), and were recommended an oral hydration so as to urinate 2 litres per day. They were cautioned to come back to the ER in the event of fever, severe nausea and vomiting, or any pain that does not respond to

Study	Uguz 2012[9]
	medication.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IMMEDIATE SHOCK WAVE LITHOTRIPSY (SWL) versus DELAYED SHOCK WAVE LITHOTRIPSY (SWL) Protocol outcome 1: Treatment success (stone free state, clinically insignificant residual fragments) at Define - Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Stone free state at 3 days; Group 1: 26/32, Group 2: 17/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Use of healthcare services/retreatment rate at Define - Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Retreatment rate at Not reported; Group 1: 6/32, Group 2: 13/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years), ureteric stone <1 cm: Ancillary procedures at Not reported; Group 1: 8/32, Group 2: 6/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; New stone formation/incidence of stones/recurrence rate at Define; Kidney function at Define; Recurrence rate at Define; Mortality at Define; Adverse events at Define; Length of stay at Define

Appendix E: Forest plots

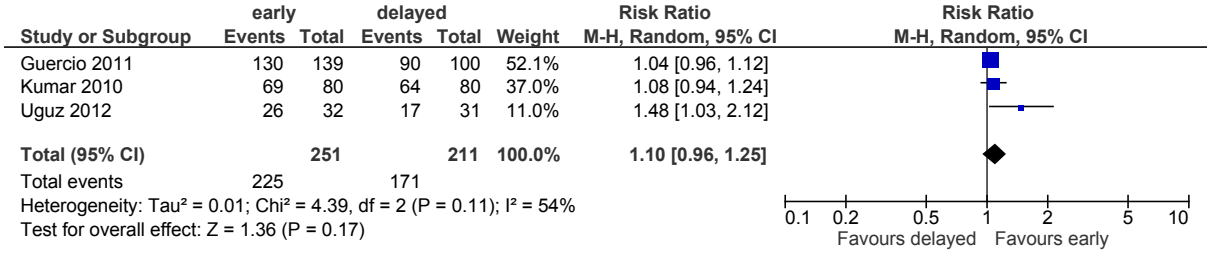
E.1 Early versus delayed intervention in people with ureteral stones in adults with ureteric stones <10mm

Figure 2: Spontaneous stone passing



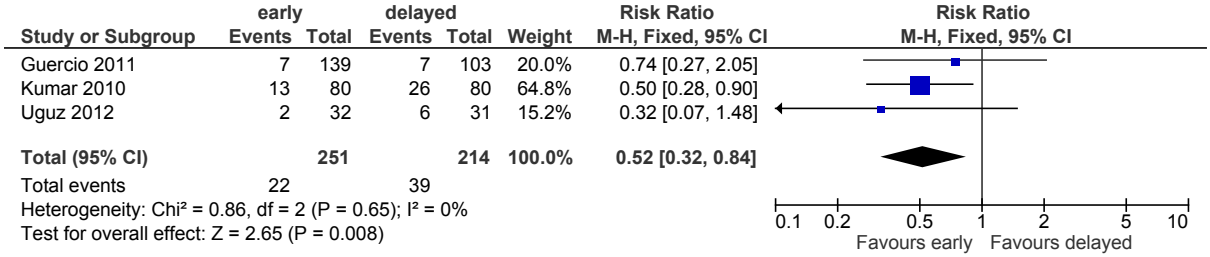
Delayed URS: median (range): 20 (15-30) days

Figure 3: Stone free rate (at 3 days – 3 months)



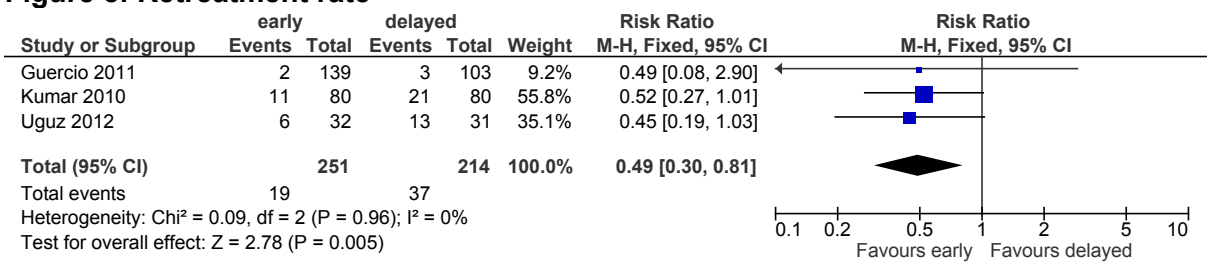
Guerico 2011: Delayed URS: median (range): 20 (15-30) days; Kumar 2010: delayed SWL: after 48 hours; Uguz 2012: delayed SWL: within 3-7 days

Figure 4: Ancillary procedure



Guerico 2011: Delayed URS: median (range): 20 (15-30) days; Kumar 2010: delayed SWL: after 48 hours; Uguz 2012: delayed SWL: within 3-7 days

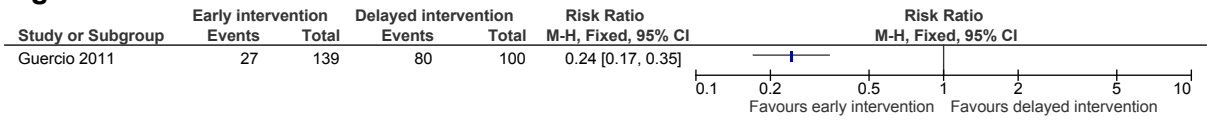
Figure 5: Retreatment rate



Guerico 2011: Delayed URS: median (range): 20 (15-30) days; Kumar 2010: delayed SWL: after 48 hours; Uguz 2012: delayed SWL: within 3-7 days

1

Figure 6: Stent insertion



Delayed URS: median (range): 20 (15-30) days

2

Appendix F: GRADE tables

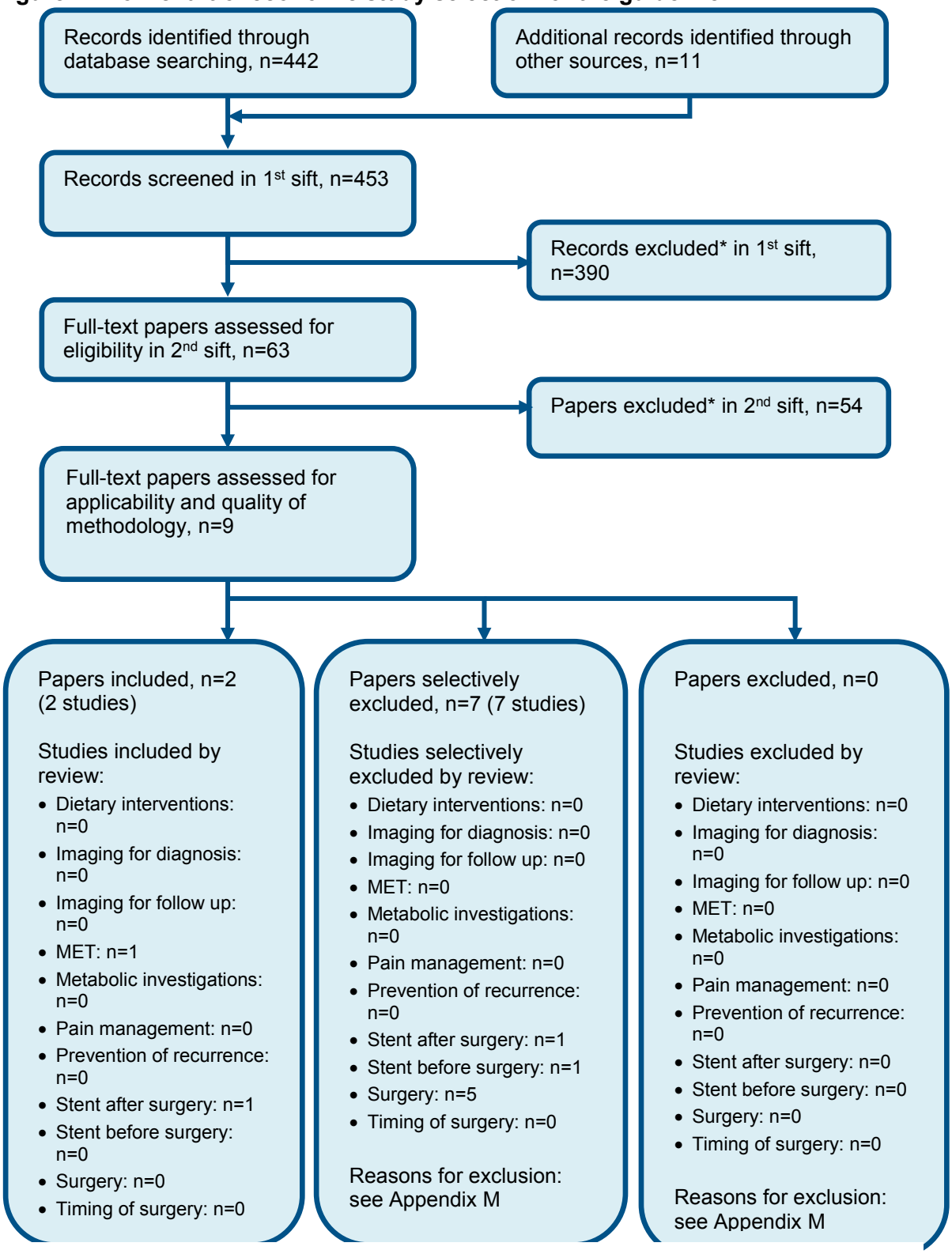
Table 9: Clinical evidence profile: early versus delayed intervention (URS)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Delayed	Relative (95% CI)	Absolute		
Stone free rate												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	225/251 (89.6%)	80%	RR 1.09 (1.01 to 1.18)	72 more per 1000 (from 8 more to 144 more)	⊕⊕OO LOW	CRITICAL
Ancillary procedures												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/251 (8.8%)	19.4%	RR 0.52 (0.32 to 0.84)	93 fewer per 1000 (from 31 fewer to 132 fewer)	⊕⊕OO LOW	CRITICAL
Retreatment rate												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19/251 (7.6%)	26.3%	RR 0.49 (0.3 to 0.81)	134 fewer per 1000 (from 50 fewer to 184 fewer)	⊕⊕OO LOW	CRITICAL
Spontaneous stone passing (follow-up 20 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/141 (0%)	5.4%	Peto OR 0.12 (0.03 to 0.53)	47 fewer per 1000 (from 25 fewer to 52 fewer)	⊕⊕OO LOW	CRITICAL
Stent insertion (follow-up 20 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/139 (19.4%)	80%	RR 0.24 (0.17 to 0.35)	608 fewer per 1000 (from 520 fewer to 664 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because heterogeneity, I2=54%, p= > 0.1, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 7: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Etemadian 2008[1]	Inappropriate comparison
Honey 2010[3]	Inappropriate comparison
Telli 2017[7]	Incorrect study design. Inappropriate comparison
Tombal 2005[8]	Inappropriate comparison
Wang 2000[10]	Inappropriate comparison

I.2 Excluded health economic studies

None