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Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function (Review)

Bell S, Rennie T, Marwick CA, Davey P

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[Intervention Review]

Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function

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ABSTRACT

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) provide effective analgesia during the post-operative period but can cause acute kidney injury (AKI) when used peri-operatively (at or around the time of surgery). This is an update of a Cochrane review published in 2007.

Objectives

This review looked at the effect of NSAIDs used in the peri-operative period on post-operative kidney function in patients with normal kidney function.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register to 4 January 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Specialised Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the use of NSAIDs versus placebo for the treatment of post-operative pain in patients with normal kidney function were included.

Data collection and analysis

Data extraction was carried out independently by two authors as was assessment of risk of bias. Disagreements were resolved by a third author. Dichotomous outcomes are reported as relative risk (RR) and continuous outcomes as mean difference (MD) together with their 95% confidence intervals (CI). Meta-analyses were used to assess the outcomes of AKI, change in serum creatinine (SCr), urine output, renal replacement therapy (RRT), death (all causes) and length of hospital stay.

Main results

We identified 26 studies (8835 participants). Risk of bias was high in 17, unclear in 6and low in three studies. There was high risk of attrition bias in six studies.

Only two studies measured AKI. The use of NSAIDs had uncertain effects on the incidence of AKI compared to placebo (7066 participants: RR 1.79, 95% CI 0.40 to 7.96; I^2 = 59%; very low certainty evidence). One study was stopped early by the data monitoring committee due

to increased rates of AKI in the NSAID group. Moreover, both of these studies were examining NSAIDs for indications other than analgesia and therefore utilised relatively low doses.

Compared to placebo, NSAIDs may slightly increase serum SCr (15 studies, 794 participants: MD 3.23 µmol/L, 95% CI -0.80 to 7.26; I^2 = 63%; low certainty evidence). Studies displayed moderate to high heterogeneity and had multiple exclusion criteria including age and so were not representative of patients undergoing surgery. Three of these studies excluded patients if their creatinine rose post-operatively.

NSAIDs may make little or no difference to post-operative urine output compared to placebo (6 studies, 149 participants: SMD -0.02, 95% CI -0.31 to 0.27). No reliable conclusions could be drawn from these studies due to the differing units of measurements and measurement time points.

It is uncertain whether NSAIDs leads to the need for RRT because the certainty of this evidence is very low (2 studies, 7056 participants: RR 1.57, 95% CI 0.49 to 5.07; I^2 = 26%); there were few events and the results were inconsistent.

It is uncertain whether NSAIDs lead to more deaths (2 studies, 312 participants: RR 1.44, 95% CI 0.19 to 11.12; I^2 = 38%) or increased the length of hospital stay (3 studies, 410 participants: MD 0.12 days, 95% CI -0.48 to 0.72; I^2 = 24%).

Authors' conclusions

Overall NSAIDs had uncertain effects on the risk of post-operative AKI, may slightly increase post-operative SCr, and it is uncertain whether NSAIDs lead to the need for RRT, death or increases the length of hospital stay. The available data therefore does not confirm the safety of NSAIDs in patients undergoing surgery. Further larger studies using the Kidney Disease Improving Global Outcomes definition for AKI including patients with co-morbidities are required to confirm these findings. .

PLAIN LANGUAGE SUMMARY

Effect of nonsteroidal anti-inflammatory medicines on kidney function in patients with normal kidney function undergoing surgery

What is the issue?

Nonsteroidal anti-inflammatory drugs (NSAIDs) offer effective pain relief following surgery. Acute kidney injury (AKI) is the rapid loss of kidney function. It is associated with high death rate. NSAIDs can lead to AKI in up to 5% of patients using them. This is increased when there are other stresses placed on the kidney such as surgery. It is therefore important to establish whether these drugs are safe to use as pain relief in patients undergoing surgery. The aim of the review was to examine whether NSAIDs lead to increased rates of AKI in patients with normal kidney function undergoing surgery. We also aimed to examine whether NSAIDs were associated with higher death rates, increased length of hospital stay and need for dialysis.

What did we do?

We updated a previous review searching the Cochrane Kidney and Transplant Specialised Register until 4 January 2018 for randomised controlled trials (RCTs) comparing NSAIDs with placebo in patients with normal kidney function undergoing surgery.

What did we find?

We identified 26 studies studying 8835 participants. Risk of bias was high in 17, unclear in six studies and low in three studies. The use NSAIDs had uncertain effects on the incidence of AKI compared to placebo. Quality of evidence was very low due to inconsistencies between the two studies. One study was stopped early by the data monitoring committee due to increased rates of AKI in the NSAID group and both of these studies examined much lower doses of NSAIDs than would usually be used for pain relief. NSAIDs may slightly increase serum creatinine (a marker of kidney function which rises in kidney failure) compared with placebo. Quality of evidence was low. These studies only included fit, healthy patients. No reliable conclusions could be drawn from the studies examining urine output due to the different methods of measuring this. It is uncertain whether the use of NSAIDs leads to an increased need for renal replacement therapy (dialysis), more deaths, or increased length of hospital stay.

Conclusions

NSAIDs have uncertain effects on the rates of AKI when used in patients with normal kidney function following surgery. It is uncertain whether NSAIDs increase the need for dialysis. The available data therefore does not confirm the safety of NSAIDs in patients undergoing surgery. Further studies including patients with other health problems are required.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus placebo or no treatment in the peri-operative period

NSAIDs versus placebo or no treatment in the peri-operative period

Patient or population: adults with normal kidney function undergoing surgery

Settings: hospitals, mainly high-income countries (North America or Western Europe)

Intervention: administration of NSAIDs in the peri-operative period

Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Intervention (NSAID)				
AKI within 30 days of surgery	**12 per 100**	**13 per 100** (12 to 14)	**RR 1.79** (0.40 to 7.96)	7066 (2)	⊕⊖⊖⊖ **very low[1]**	NAFARM 2011 was stopped by study monitoring committee because of increased risk of AKI. Both studies used NSAID doses that were much lower than would be used for analgesia in usual care. The results raise serious concerns about the safety of post-operative analgesia with NSAIDs in unselected patients
SCr increase within 30 days of surgery	The mean difference in SCr in control group was decreased by -2.60 µmol/L	The mean difference in SCr in the intervention group was increased by 1.52 µmol/L (-7.4 to 10.2)	Difference in post-operative SCr increased by 3.23 µmol/L (-0.8 to 7.26)	794 (15)	⊕⊕⊖⊖ **low[2]**	Heterogeneity was not explained by pre-specified effect modifiers (Table 1, Figure 1)
RRT within 30 days of surgery	**2 per 1000**	**5 per 1000** (2 to 11)	**RR 1.57** (0.49 to 5.07)	7056 (2)	⊕⊖⊖⊖ **very low[3]**	--
Death (all causes)	**2 per 100**	**3 per 100**	**RR 1.44** (0.19 to 11.12)	312 (2)	⊕⊖⊖⊖ **very low[3]**	--

		(0 to 6)				
Length of hospital stay	The mean length of hospital stay in control group was 10.0 days	The mean length of hospital stay in the intervention group was 10.6 days (range 5.3 to 18.33)	**MD 0.12** (-0.48 to 0.72)	410 (3)	⊕⊖⊖⊖ **very low[3]**	--

*The basis for the **assumed risk** is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **MD:** mean difference; **AKI:** acute kidney injury; **SCr:** serum creatinine; **RRT:** renal replacement therapy

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

The assumed risk is the median or mean across the control groups for each intervention
[1] 1 downgrade for study limitations, one for imprecision, and one for heterogeneity (Appendix 3).
[2] We downgraded the certainty of evidence to low because of inconsistency and indirectness (Appendix 3).
[3] We downgraded the certainty of evidence to very low because of risk of bias, imprecision, inconsistency and indirectness (Appendix 3).

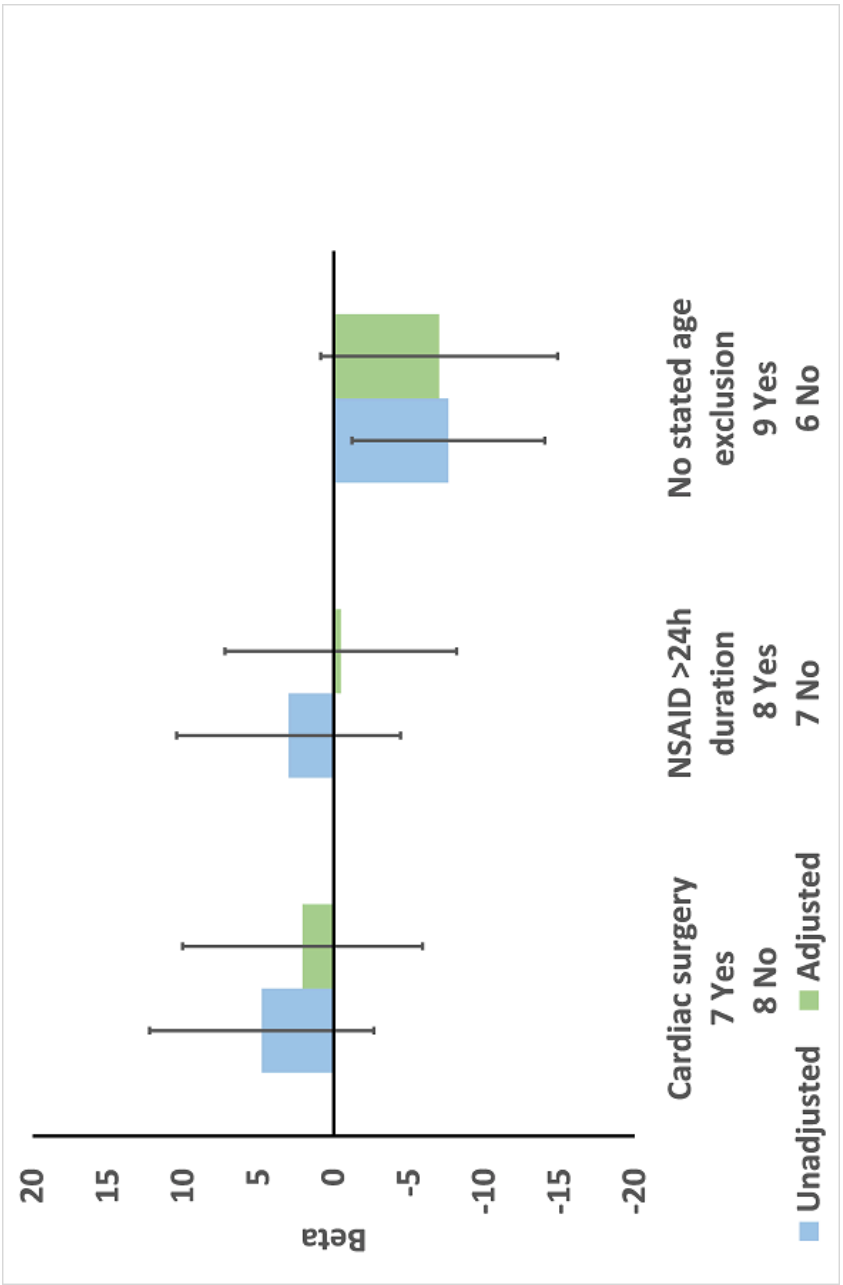


Figure 1. Meta-regression of change in post-operative serum creatinine (Analysis 2.1) by type of surgery, duration of NSAID use, and exclusion by age. Results are Beta with 95% CI. A positive value for Beta indicates that a variable is associated with increased effect size.

BACKGROUND

Description of the condition

There is increasing evidence that acute kidney injury (AKI) is associated with both short- and long-term adverse consequences. These include increased length of hospital stay, death and future development of chronic kidney disease (CKD) even with small transient rises in serum creatinine (SCr) (Bucaloiu 2012; Chertow 2005; Coca 2012; Lassnigg 2004). Surgery is a leading cause of AKI in hospitalised patients (Carmichael 2003). There was previously significant variation in defining AKI. These included changes in SCr, urine output and creatinine clearance (CrCl). The Kidney Disease Improving Global Outcomes (KDIGO) definition has been universally accepted since 2012 KDIGO 2012.

Effective management of post-operative pain is extremely important. It facilitates early mobilisation thereby reducing hospital costs through shortened duration of hospital in-patient stay, reduces pulmonary and cardiovascular complications and risk of deep vein thrombosis. In addition, it impacts on quality of patient care by relieving suffering and distress and improving satisfaction. The major aim of post-operative pain management is providing adequate pain relief using the minimal possible dose thereby minimising adverse effects. Clinical guidelines for managing perioperative pain by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council were published in 2016 (Chou 2016). They recommend a multimodal approach to post-operative pain including the use of both nonselective nonsteroidal anti-inflammatory drugs; (NSAIDs) as well as selective NSAIDs (Cox-2 inhibitors). NSAIDs can affect the kidneys in a number of ways. This includes haemodynamically mediated AKI, electrolyte and acid-base disorders and acute interstitial nephritis. These adverse effects are thought to occur in 1% to 5% of all patients using NSAIDs (Whelton 1999).

Description of the intervention

NSAIDs inhibit prostaglandin synthesis by inhibiting cyclooxygenase-1 (Cox-1) and cyclooxygenase -2 (Cox-2). Cox-1 is expressed in most tissues regulating normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. Cox-2 is expressed in brain, kidney and bone. Most traditional NSAIDs are non-selective inhibitors of both Cox-1 and Cox-2. Selective Cox-2 inhibitors include celecoxib, rofecoxib and valdecoxib.

Cyclooxygenases are produced at multiple sites within the kidney including glomerular and vascular endothelium, medullary and cortical collecting tubules and medullary interstitial cells. Cox-1 is expressed in most tissues and Cox-2 is expressed at low levels increasing with stimulation such as inflammation. Renal prostaglandins are primarily vasodilators in the kidneys. Under normal circumstances, renal prostaglandins do not contribute to regulation of kidney perfusion but in the setting of hypotension and reduced kidney perfusion from vasoconstriction prostaglandin synthesis is increased to maintain kidney perfusion and minimize ischaemia. Other kidney effects of prostaglandins include increased renin secretion, antagonism of anti-diuretic hormone effects and increased sodium excretion.

How the intervention might work

The use of both non-selective and selective NSAIDs for post-operative pain has been evaluated in a number of Cochrane reviews. A single dose of ibuprofen lead to at least 50% pain relief in approximately half of patients with moderate to severe post-operative pain. Adverse effects were similar to placebo (Derry 2009). Aspirin was found to confer a 50% or greater reduction in pain in 39% of those with moderate to severe pain, compared with 15% of those in the placebo group. Adverse events were similar for those taking a lower dose aspirin (600 mg or 650 mg). However, higher dose aspirin (900 mg to 1000 mg) experienced adverse events at more than twice the rate of patients receiving placebo (26% versus 12%) (Derry 2012a). The use of a single dose of the Cox-2 inhibitor celecoxib in the treatment of acute post-operative pain showed that 33% of patients receiving celecoxib 200 mg, and 44% receiving 400 mg, experienced at least 50% pain relief, compared with between 1% and 11% of patients receiving placebo. Adverse events were similar in the celecoxib and placebo groups (Derry 2012b).

Furthermore, there is evidence supporting the efficacy of NSAIDs for post-operative pain with studies demonstrating opioid sparing effects (McDaid 2010).

NSAIDs have the potential to adversely affect kidney function in the peri-operative setting. Pre-renal insults such as hypovolaemia or hypotension peri-operatively cause NSAID-induced inhibition of prostaglandin mediated afferent arteriolar dilatation leading to reduced glomerular perfusion. The risk of AKI with NSAIDs has led the Medicines and Healthcare Products Regulatory Agency to issue drug safety advice recommending that NSAIDs be avoided in patients with hypovolaemia (MHRA 2009). Other adverse events associated with NSAIDs include gastrointestinal bleeding and cardiovascular events. These were not examined in this review.

Why it is important to do this review

This is an update of a Cochrane review last published in 2007 (Lee 2007). This review showed that NSAIDs caused a clinically unimportant transient reduction in kidney function in the early post-operative period in patients with normal kidney function. Since its publication, a universal definition for AKI has been developed allowing a better understanding of its epidemiology and clinical significance (KDIGO 2012). Since the advent of the KDIGO definition for AKI, there is increasing evidence of the adverse clinical and economic consequences of AKI. In addition, National Institute for Clinical Excellence (NICE) AKI guidance recommends the avoidance of NSAIDs in the post-operative period (Ftouh 2013).

It is therefore important to re-assess the renal safety of NSAIDs in the peri-operative period.

OBJECTIVES

This review looked at the effect of NSAIDs used in the peri-operative period on post-operative kidney function in patients with normal kidney function.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the use of NSAIDs versus placebo in the post-operative phase in adults with normal kidney function were included.

Types of participants

People of at least 18 years of age undergoing surgical procedures who were treated with NSAIDs or Cox-2 inhibitors with normal kidney function were included. Normal kidney function was defined as estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 mm^2 without other evidence of kidney disease (proteinuria, haematuria, genetic kidney disease or structural kidney abnormalities).

Types of interventions

All interventions comparing NSAID treatments including Cox-2 inhibitors versus placebo were considered. Variable doses, all routes of administration and variable indications for NSAID use were considered.

Types of outcome measures

The primary endpoint was AKI. Studies measuring SCr and urine output in the post-operative phase were also considered. The secondary outcomes of length of hospital stay, death and requirement of renal replacement therapy (RRT) were documented when available.

Primary outcomes

The primary outcome was AKI as defined by KDIGO which is based on SCr or urine output (KDIGO 2012). Change in SCr and urine output were also considered using the highest post-operative creatinine or lowest post-operative urine volume. These were analysed separately.

Secondary outcomes

1. Need for RRT
2. Death (all causes)
3. Length of hospital stay

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 4 January 2018 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable, however studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data were used in the analyses. Data extracted included study design, inclusion and exclusion criteria, patient numbers and characteristics and treatment regimen. For outcomes of interest (AKI, serum, creatinine, urine output, death, need for RRT and length of hospital stay), the raw data were extracted using mean, median and standard deviations for continuous outcomes, and event rate for dichotomous outcomes. Where data were collected at more than one time-point, these were all extracted. Peak SCr and lowest urine volume were used for the analyses.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?

- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

In each domain, studies were labelled as low, high or unclear risk of bias with consideration given to the presence or absence of sufficient information to make a determination. Reasons for assessment were documented (See Characteristics of included studies), and a risk of bias summary is presented.

Measures of treatment effect

For the dichotomous outcomes (presence of AKI, need for RRT and death), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Continuous scales of measurement such as mean difference (MD) and 95% CI was used to assess the effects of treatment for change in SCr and length of hospital stay. SCr was converted to standardised units (µmol/L) and peak post-operative creatinine was used when more than one post-operative creatinine was reported. Mean change in SCr was not given in studies and so the correlation coefficient between pre and post-operative measures were not known. We therefore assumed a correlation coefficient of 0.50 (Follmann 1992). A sensitivity analysis was carried out assuming zero correlation. The standard deviation between pre and post-operative measures for each treatment group was estimated using a method outlined in the Cochrane Collaboration Handbook. When the median and interquartile range were reported, we assumed that the mean was equivalent to the median and estimated the standard deviation to be the interquartile range/1.35 (O'Rourke 2002). Standardised mean difference (SMD) was used for urine output as different scales were used. Lowest post-operative urine output was used when more than one time point was measured.

In studies comparing multiple different NSAIDs or varying dosing regimens, the dose or dug with the greatest adverse effect on kidney function was included in the analysis.

Unit of analysis issues

Studies with non-standard designs, such as cross-over studies and cluster-randomised studies were not included in this review.

Dealing with missing data

We did not contact any authors as the required information was present in the studies. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Meta-regression was carried out to investigate possible explanations for heterogeneity of effects, including type of surgery (cardiac versus other), duration of NSAID therapy (>24h versus <24h) and whether age was an exclusion criterion (no versus yes) as potential explanatory variables. Meta-regression used standard weighted (by standard error of estimate) linear regression in IBM SPSS Statistics 22.

Sensitivity analysis

We planned to perform sensitivity analyses if there were sufficient studies identified, in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

We were only able to investigate the influence of risk of bias on effect size due to the number of studies identified. The analysis was repeated excluding studies with high risk of bias, attrition bias or high risk of bias or attrition bias.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented

the following outcomes in Summary of findings for the main comparison.

- AKI within 30 days of surgery
- Mean difference in SCr increase in µmol/L within 30 days of surgery
- RRT within 30 days of surgery
- Death (all causes)
- Length of hospital stay (days)

RESULTS

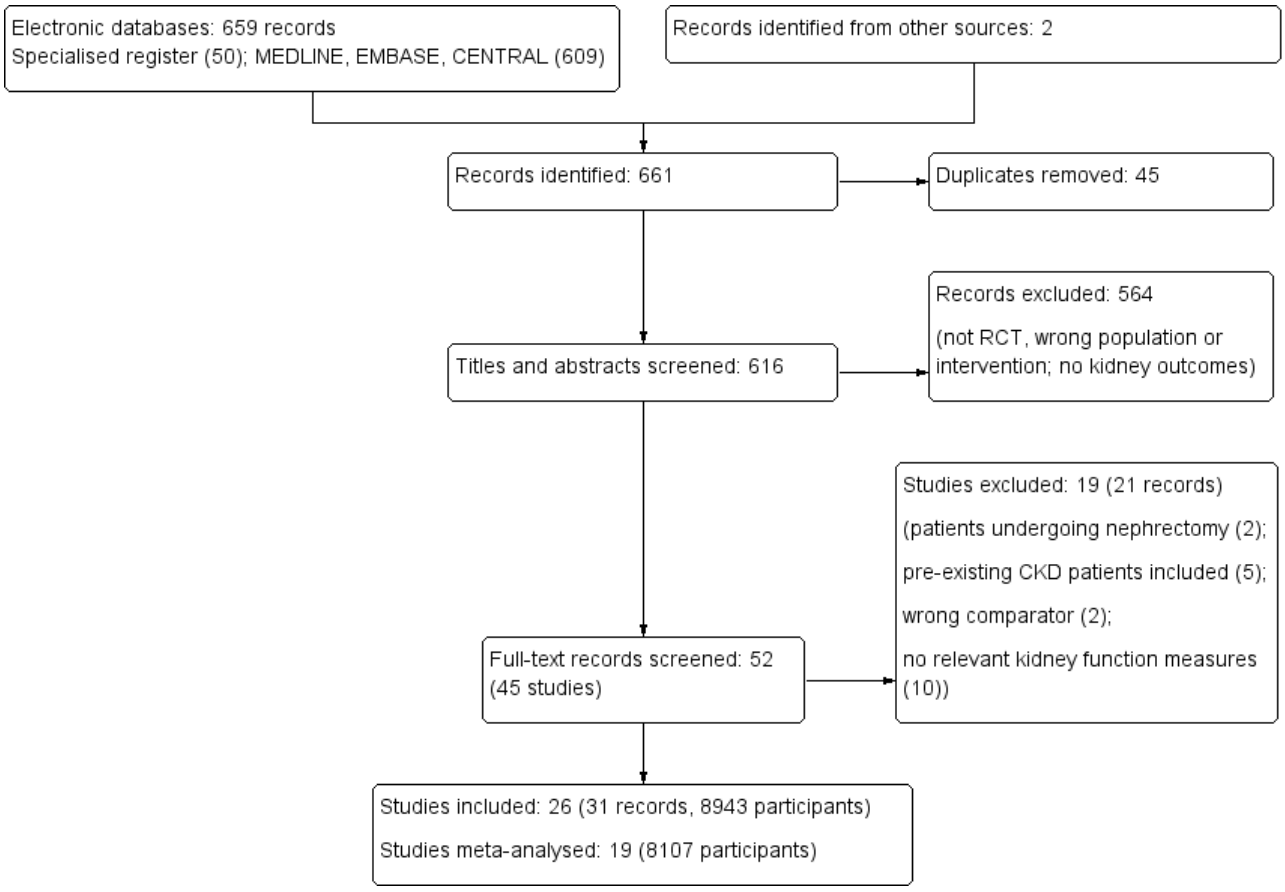
Description of studies

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

In total 659 records were identified through database searches, and two records were added through other means. Forty-five records were duplicates and were excluded. The titles and abstracts of the remaining 616 records were reviewed by two independent assessors and 52 records were deemed eligible for full text review. Nineteen records (21 studies) were excluded; details about the reason for exclusion can be found in the table Characteristics of excluded studies. The remaining 31 records (26 studies) were included (see Figure 2).

Figure 2. Study flow diagram.



Included studies

Twenty-six studies (8943 patients) met our inclusion criteria. A detailed overview of all the included studies can be found in the Characteristics of included studies table. The studies were conducted between 1992 and 2017 and included adults with preserved kidney function prior to surgery. Of these, 19 (8107 participants) could be meta-analysed.

Six studies (Chow 2001; Castiglione 1997; Nuutinen 1991; Parker 1994; Ready 1994; Rao 2000) included in the previous version of this review (Lee 2007), were not included in our review. One study enrolled patients who underwent a nephrectomy (Chow 2001); one study used NSAID in both groups (Castiglione 1997); and four studies were excluded due to the absence of concise post-operative kidney outcomes in these studies (Nuutinen 1991; Parker 1994; Ready 1994; Rao 2000) – in line with the KDIGO diagnostic AKI criteria (KDIGO 2012).

Nine new studies (Eljezi 2017; Fayaz 2004; Koppert 2006; McCrory 2002; NAFARM 2011; Ott 2003; POISE-2 2013; Puolakka 2009; Rafiq 2014) were added to this review.

Types of surgery

Patients underwent various types of surgery: 13 studies reviewed patients undergoing open cardiac surgery (Eljezi 2017; Fayaz 2004; Hynninen 2000; Immer 2003; Khalil 2006a; Kulik 2004; McCrory 2002; NAFARM 2011; Ott 2003; Perttunen 1992; Perttunen 1999; Rafiq 2014; Rapanos 1999) and six studies reviewed abdominal or pelvic surgeries (Aitken 1992; Jones 2000; Power 1992; Puolakka 2009; Turner 1994; Varrassi 1994). The remainder of the studies reviewed patients undergoing orthopaedic, breast, and various other non-cardiac surgeries.

Interventions

NSAIDs included in the study were ketorolac (Aitken 1992; Laisalmi 2001a; Perttunen 1992; Perttunen 1999; Rafiq 2014; Varrassi 1994), indomethacin (Hynninen 2000; Rapanos 1999; Turner 1994), diclofenac (Fayaz 2004; Hynninen 2000; Immer 2003; Irwin 1995; Perttunen 1992; Perttunen 1999; Power 1992), aspirin (POISE-2 2013), ibuprofen (Brinkmann 1998; McCrory 2002; Rafiq 2014), naproxen (Kulik 2004), tenoxicam (Jones 2000; Slaven 1998), etodolac (Immer 2003), and ketoprofen (Eljezi 2017). Selective COX-2 inhibitors were used in four studies (Khalil 2006a; Koppert 2006; Ott 2003; Puolakka 2009).

Mode of delivery was via intravenous (IV) or intramuscular (IM) injection in 15 studies (Aitken 1992; Brinkmann 1998; Eljezi 2017; Jones 2000; Khalil 2006a; Koppert 2006; Kostamovaara 1996; Laisalmi 2001a; Perttunen 1992; Perttunen 1999; Power 1992; Puolakka 2009; Slaven 1998; Varrassi 1994). A combination of an IV bolus and oral maintenance dose was used by Ott 2003 and Rafiq 2014. The remaining studies used either oral, epidural or per rectum administration methods. Seven studies prescribed NSAIDs for the first post-operative day only (Fayaz 2004; Hynninen 2000; Irwin 1995; Laisalmi 2001a; Puolakka 2009; Rapanos 1999; Varrassi 1994). The median duration of post-operative NSAID exposure was 2 days (range 1 to 30 days).

Measurement of primary outcomes

One study defined AKI using the KDIGO definition (POISE-2 2013) and one using an elevation in SCr of 150% times the baseline (NAFARM 2011). Creatinine was measured in 15 studies (Immer 2003; Koppert 2006; Kostamovaara 1996; Kulik 2004; Laisalmi 2001a; Ott 2003; Perttunen 1992; Perttunen 1999; POISE-2 2013; Power 1992; Puolakka 2009; Rafiq 2014; Rapanos 1999; Turner 1994; Varrassi 1994). A percentage change in creatinine from baseline was reported by Eljezi 2017. Change in urine output post-operatively was reported by seven studies (Aitken 1992; Eljezi 2017; Irwin 1995; Jones 2000; Laisalmi 2001a; Perttunen 1992; Perttunen 1999). Serum creatinine clearance was measured by one study (Brinkmann 1998) and urinary creatinine clearance by four studies (Khalil 2006a; Koppert 2006; McCrory 2002; Slaven 1998).

Measurement of secondary outcomes

Death (all causes) was reported by two studies (NAFARM 2011; Rafiq 2014); hospital stay by three studies (NAFARM 2011; Kulik 2004; Rafiq 2014), and two studies reported the need for RRT post-operatively (Rafiq 2014; POISE-2 2013).

Excluded studies

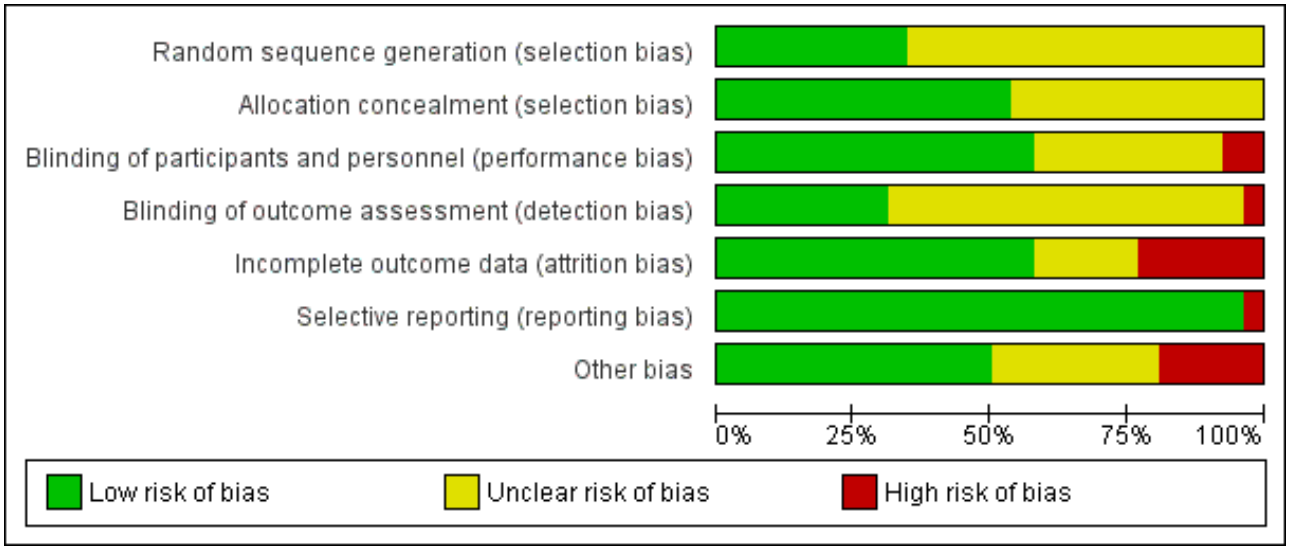
Nineteen studies (21 records) were excluded from this review. Details of the reason for exclusion for all of these are found in the Characteristics of excluded studies table.

Four studies were excluded due to the inclusion of patients with pre-existing CKD into their cohort (Cheruku 2004; Merry 2002; Nussmeier 2005; Nussmeier 2006). Two studies published results about kidney function after nephrectomy (Chow 2001; Grimsby 2012) and were deemed unsuitable for analysis in our review. Eleven studies were excluded due to lack of concise post-operative kidney outcomes (Daniels 2014; Fredman 1999; Hynes 2006; Leeson 2007; Ma 2015; Nuutinen 1991; Parker 1994; Rao 2000; Ready 1994; Southworth 2009; Varrassi 1999). Two studies were not suitable for inclusion in this review due to the lack of a suitable placebo group (Castiglione 1997; Doyle 1998).

Risk of bias in included studies

See Figure 3.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Nine studies were assessed as low risk, with sufficient information about the sequence generation process (Fayaz 2004; Jones 2000; Khalil 2006a; Kulik 2004; NAFARM 2011; Perttunen 1999; POISE-2 2013; Puolakka 2009; Rapanos 1999). Most commonly described sequence generation method was computer software. In the remaining 17 studies randomisation was stated but no information was given about the method of sequence generation.

Allocation concealment

Fourteen studies described a randomisation method that was deemed adequate; investigators or participants did not know or have influence on the intervention group before entering the study (Eljezi 2017; Fayaz 2004; Hynninen 2000; Jones 2000; Khalil 2006a; Koppert 2006; Kulik 2004; NAFARM 2011; Perttunen 1999; POISE-2 2013; Puolakka 2009; Rafiq 2014; Rapanos 1999; Turner 1994). Most commonly used method was sequentially numbered opaque, sealed envelopes. The remaining 12 studies did not provide enough information to determine the method of allocation concealment.

Blinding

Performance bias

All studies mentioned blinding of participants, investigators or both in their methods section, however in nine studies insufficient information was provided regarding the methods by which this was achieved. For that reason those studies were assessed as unclear risk of performance bias due to the knowledge of the allocated interventions by participants and personnel during the study (Aitken 1992; Brinkmann 1998; Immer 2003; Irwin 1995; Kostamovaara 1996; Laisalmi 2001a; Ott 2003; Power 1992; Varrassi 1994). Two studies were open-label and were judged to be at high risk of bias (McCrory 2002; Rafiq 2014). The remaining 15 studies were judged to be a low risk of bias.

Detection bias

Seven studies were judged to be at low risk bias (Jones 2000; Kulik 2004; NAFARM 2011; Perttunen 1992; Perttunen 1999; POISE-2 2013; Turner 1994). One study was classed as high risk of detection bias (Rafiq 2014), and for the remaining 18 studies risk of detection bias was judged to be unclear.

Incomplete outcome data

Patient drop-out was reported in 16 studies.

- Protocol violation or equipment failure was the cause of the drop-out in seven studies (Aitken 1992; Irwin 1995; Koppert 2006; Ott 2003; Rafiq 2014; Rapanos 1999; Turner 1994).
- Side effects of the treatment or complications of the surgery was the cause for drop-out in five studies (Eljezi 2017: 3 patients dropped out due to complications of the surgery, reintubation and/or re-surgery; Kostamovaara 1996: 1 patient dropped out due to side effect of fentanyl administration, no side effects of the study drug ketorolac were identified; Kulik 2004: 2 patients in the naproxen group and 4 patients in the placebo group suffered from complications after surgery; Rafiq 2014: 21 patients had a prolonged stay in intensive care post surgery - equally distributed between groups; Varrassi 1994: 5 patients withdrew due to re-laparotomy or inadequate pain control, equally distributed over the two groups).
- NAFARM 2011 reported death due to cardiac surgery as the cause of drop-out in five patients.
- Oliguria or rise in creatinine post operatively was identified as cause for withdrawal in six studies (Fayaz 2004; Hynninen 2000; Immer 2003; Kulik 2004; Power 1992; Rafiq 2014) affecting eight patients in total. This is a significant cause for concern as only three of these studies (Hynninen 2000; Immer 2003; Rafiq 2014) acknowledged the potential effect of the study medication on kidney function in their conclusion.

Six studies were deemed high risk of attrition bias due to missing data which potentially has a significant effect on the overall outcome of the study. Aitken 1992 failed to present the reader

with a reason for missing urine output data in 15 of 61 patients, while 26% of patients were withdrawn from Ott 2003; mainly due adverse events. Oliguria and/or rise in creatinine post-operatively was identified as cause for withdrawal from the study in six studies. Four of these studies (Fayaz 2004; Immer 2003; Kulik 2004; Power 1992) were deemed high risk of bias since these patients who were particularly at risk of developing AKI (the primary outcome of this review) were withdrawn from the studies. Hynninen 2000 also withdrew one patient after one dose of indomethacin because of SCr increase > 20% post-operatively. This patient did not receive further NSAIDs as per protocol. This study was classed as low risk as the patient was not included in the post-operative outcome table and the plausible effect size of this one event is probably not enough to have a clinically relevant impact on observed effect size.

Fifteen studies were judged to be a low risk of attrition bias (Eljezi 2017; Hynninen 2000; Irwin 1995; Jones 2000; Khalil 2006a; Koppert 2006; Kostamovaara 1996; Laisalmi 2001a; NAFARM 2011; Perttunen 1999; POISE-2 2013; Puolakka 2009; Rafiq 2014; Rapanos 1999; Varrassi 1994). The risk of attrition bias was unclear in the remaining five studies.

Selective reporting

Twenty-five studies reported the outcomes that were prespecified in their methods. Eljezi 2017 failed to report the frequency of urinary output (4-hourly for 48 hours) and creatinine measurements (baseline, post-operative day 1 and 2) as they had set out to do in the methods section. Urinary output was documented at 48 hours only and a percentage change in SCr at 48 hours from baseline was reported. This study was classed as high risk for reporting bias as it is unclear whether a potential transient fall in urine output and rise in creatinine during the first post-operative day has occurred, which would significantly change the conclusion drawn from this report.

Other potential sources of bias

Eleven studies reported to have received either no funding or funding from a non-profit organisation and were therefore deemed at low risk of publication bias (Eljezi 2017; Kostamovaara 1996; Kulik 2004; Laisalmi 2001a; McCrory 2002; NAFARM 2011; Perttunen 1992; Perttunen 1999; Puolakka 2009; Rafiq 2014; Rapanos 1999). POISE-2 2013 used several sources of funding; firstly two large governmental non-profit organisations from Spain and Australia. Secondly an undefined amount of financial support as well as study drugs from a commercial body were disclosed. The authors state that the sponsors had no role in the design and conduct of the study, collection, management, analysis, review or approval of the manuscript; and decision to submit the manuscript for publication. Due to the combination of commercially as well as non commercially accrued funding sources used in this study, in combination with the extensive disclosure of the use of the commercially acquired funding, this study was classed as low risk. Slaven 1998 received the study drug and placebo as a gift from the manufacturer, however the study design and analysis of the results was independent of any company involvement and was judged to be at low risk of bias.

Six studies were classed as high risk of bias due to the use of commercial funding. An unknown quantity of financial support from a commercial body was received by three studies (Jones 2000; Khalil 2006a; Koppert 2006). Aitken 1992 received financial support as well as study drugs from a pharmaceutical company. Commercially provided study drugs were used by Immer 2003. Other potential biases were unclear in the remaining eight studies.

Effects of interventions

See: **Summary of findings for the main comparison** Nonsteroidal anti-inflammatory drugs (NSAIDs) versus placebo or no treatment in the peri-operative period

See Summary of findings for the main comparison for main comparisons.

Post-operative acute kidney injury

One large study (6905 participants) POISE-2 2013 reported AKI defined by the KDIGO criteria and one smaller study (161 participants) NAFARM 2011 defined AKI as a rise of SCr of 150% times the baseline. The use of NSAIDs had uncertain effects on the incidence of AKI compared to placebo (Analysis 1.1 (2 studies, 7066 participants): RR 1.79, 95% CI 0.40 to 7.96; I^2 = 59%; very low certainty evidence). The analysis was dominated by POISE-2 2013 with 70.4% of the weighting and medium level of heterogeneity. NAFARM 2011 was terminated early by the trial monitoring committee because of increased risk of AKI.

Post-operative serum creatinine

Change in SCr was reported in 15 studies. AKI is defined as peak post-operative SCr and so where creatinine was measured over several time points, peak SCr was used for the analysis. In addition, where several different NSAIDs or dosing regimens were compared in a study, the regime or drug with the greatest adverse effect on kidney function was included within the analysis. Ott 2003 defined kidney dysfunction as a creatinine value > 177 µmol/L and an increase of 62 µmol/L with an incidence of 2.6% in both groups. This study was not included in the pooled analysis due to the lack of absolute values.

Compared to placebo, NSAIDs may slightly increase serum SCr (Analysis 2.1 (15 studies, 794 participants): MD 3.23 µmol/L, 95% CI -0.80 to 7.26; I^2 = 66%; low certainty evidence). Heterogeneity was medium to high.

Meta-regression of change in post-operative serum creatinine by pre-specified effect modifiers

Of the 15 studies in the meta-analysis of change in post-operative SCr (Analysis 2.1), seven studies were in cardiac surgery, eight with > 24 hours of NSAID use, and nine with no stated age exclusion (Table 1). As expected cardiac surgery and > 24 hours of NSAID use were associated with a positive beta (greater effect size) in the meta-regression (Figure 1). In contrast, we expected that RCTs with no stated age exclusion would have greater effect size but beta was negative (lower effect size) for these RCTs in the univariate meta-regression (Figure 1). Multivariate analysis did not identify significant effect modifiers (Figure 1).

Sensitivity analyses

Exclusion of studies with an overall high risk of bias (Analysis 2.2), high risk of attrition bias (Analysis 2.3) and either high overall risk of bias or high risk of attrition bias (Analysis 2.4) reduced the effect estimate.

Post-operative urine output

Change in urine output was measured in seven studies. Eljezi 2017 measured urine output at 48 hours but did not report baseline urine output. Where urine output was measured over several time points, lowest post-operative urine output was used for the analysis. Urine output was measured as total volume, mL/min and mL/kg/h therefore standardised mean difference (SMD) was used for pooling the data.

NSAIDs may make little or no difference to post-operative urine output compared to placebo (Analysis 3.1 (6 studies, 149 participants): SMD -0.49, 95% CI -1.21 to 0.24; I^2 = 77%; low certainty evidence) Heterogeneity was high. The differences in units of measurements and time points when urine output was measured in the different studies rendered interpretation of these results difficult.

Need for renal replacement therapy

Two studies reported the need for RRT (POISE-2 2013; Rafiq 2014). It is uncertain whether NSAIDs leads to the need for RRT because the certainty of this evidence is very low (Analysis 4.1 (2 studies, 7056 participants): RR 1.57, 95% CI 0.49 to 5.07; I^2 = 26%). Heterogeneity was low.

Death (all causes)

Two studies reported death (NAFARM 2011; Rafiq 2014). It is uncertain whether NSAIDs leads to more deaths because the certainty of this evidence is very low. These were two small studies with a small number of events (Analysis 5.1 (2 studies, 312 participants): RR 1.44, 95% CI 0.19 to 11.12; I^2 = 38%) Heterogeneity was low to medium.

Length of hospital stay

Three studies examined length of hospital stay (NAFARM 2011; Kulik 2004; Rafiq 2014). It is uncertain whether NSAIDs result in a longer hospital stay because the certainty of this evidence is very low (Analysis 6.1 (3 studies, 410 participants): MD 0.12 days, 95% CI -0.48 to 0.72; I^2 = 24%). Heterogeneity was low.

DISCUSSION

Summary of main results

We included 26 eligible studies (8943 participants) examining the use of NSAIDs in the perioperative period in patients with normal kidney function. The primary outcome of AKI, defined by KDIGO creatinine-based criteria, was used in only two studies. Change in SCr was measured in 14 studies and urine output in seven. For the secondary outcomes, two studies examined RRT, two examined death, and two length of hospital stay. Type of surgery, duration of treatment and dosage varied among the studies. Kidney outcomes were secondary outcomes in 13 studies. Two studies examined the use of NSAIDs for indications other than analgesia (NAFARM 2011; POISE-2 2013) and the NSAID doses were lower than would be used as analgesia. Overall risk of bias was high in 17, unclear in six studies and low in three studies. Overall NSAIDs had uncertain effects on the risk of post-operative AKI, may slightly increase post-operative SCr, and it is uncertain whether NSAIDs leads to the need for RRT, death or increases the length of hospital stay (Summary of findings for the main comparison)

The two studies with AKI as a primary outcome were the largest studies in the review and had few exclusions (NAFARM 2011; POISE-2 2013). One study was stopped by the data monitoring committee because of increased risk of post-operative AKI in the NSAID group (NAFARM 2011). The indication for NSAID use was to reduce risk of post-operative atrial fibrillation. The dose of naproxen (550 mg/d) was below the lowest daily dose recommended for analgesia for osteoarthritis (750 mg/d; Chou 2011) and substantially lower than the dose of 1000 mg/d used for post-operative analgesia in another study in our review (Kulik 2004). The contrast between the results of NAFARM 2011 and Kulik 2004 is striking. Both studies used the same NSAID (naproxen) for the same duration (four days) in the same patient group (coronary artery bypass graft surgery). However, despite using a much lower dose of naproxen, NAFARM 2011 was stopped because of increased risk of post-operative AKI whereas Kulik 2004 reported that naproxen use was associated with a mean decrease in post-operative SCr. POISE-2 2013 aimed to reduce the risk of post-operative AKI in patients undergoing elective or emergency surgery and included 6905 patients from 22 countries. The aspirin group received 200 mg on the day of surgery and then 100 mg/d for seven days, whereas the maximum recommended daily dose of aspirin is 4000 mg (NICE 2017).

Compared to placebo, NSAIDs may slightly increase serum SCr (3.23 µmol/L, 95% CI -0.80 to 7.26). Studies displayed moderate to high heterogeneity with multiple different exclusion criteria (e.g. age, diabetes, heart failure, use of diuretics) and so were not representative of patients undergoing surgery. Three of these studies excluded patients if their creatinine rose post-operatively.

No reliable conclusions could be drawn from the studies examining urine output due to the differing units of measurements and measurement time points.

It is uncertain whether the use of NSAIDs leads to an increased need for RRT, more deaths, or increased length of hospital stay.

Overall completeness and applicability of evidence

There are significant limitations to this review. Most of the studies excluded patients with co-morbidities such as diabetes, heart, liver, or respiratory failure. The population studied was therefore highly selected and non-representative of the population of patients undergoing surgery in most hospitals. With the exception of one study (POISE-2 2013), the studies were small and heterogeneous examining various types of NSAIDs, various doses and different types of surgery. A further important limitation was that three studies (Fayaz 2004; Hynninen 2000; Immer 2003) excluded patients if their SCr rose post-operatively and one study (Power 1992) administered furosemide to patients if their post-operative urine output fell. This impacts on the outcomes of these studies as they included both SCr and urine output.

The largest study (POISE-2 2013) examined the kidney effects of aspirin for an indication other than analgesia in 6905 patients undergoing surgery. Types of surgery included major vascular, thoracic, urological, and gynaecological. Patients with co-morbidities such as diabetes and cardiovascular disease were included. There were also patients with CKD included. Patients received aspirin at very low dose (100 mg/d; NICE 2017) and was associated with an uncertain effect on post-operative AKI (Analysis 1.1) and RRT (Analysis 4.1). The risk difference for RRT was 3 patients

per 1000 treated (95% CI 0 to 6). Inclusion of this large study impacted significantly on the findings of this review.

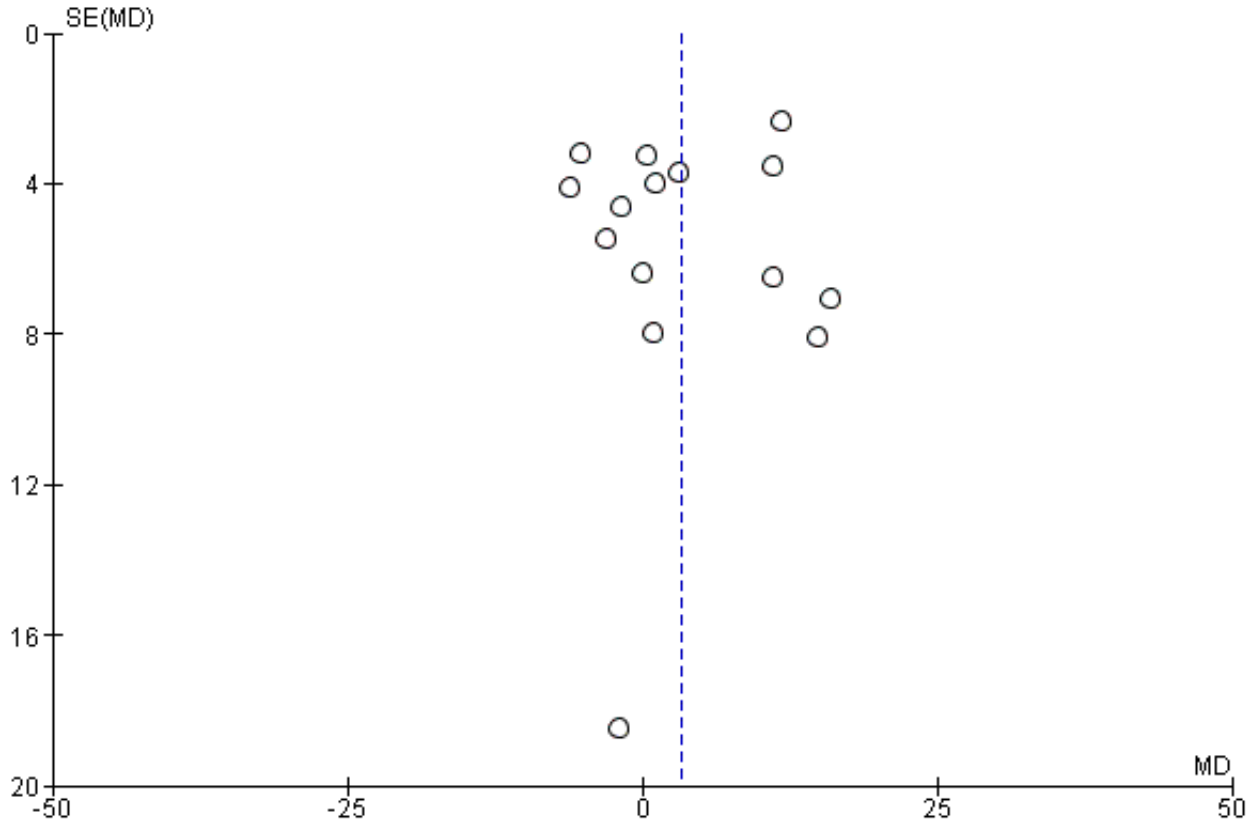
Quality of the evidence

We identified 26 eligible RCTs with 8835 participants examining the use of NSAIDs in the perioperative period in patients with normal kidney function. Risk of bias was high in 17, unclear in 6studies and low in 3 studies with high risk of attrition bias in 6 studies.

We have graded the evidence that NSAIDs increase the risk of post-operative AKI as very low certainty (Summary of findings for the main comparison). These were the largest RCTs in the review and both were low risk of bias (NAFARM 2011, POISE-2 2013). Importantly, both trials included patients with co-morbidities and both studies used NSAIDs at relatively low doses for non-analgesic indications. Our main concern was about the inconsistencies between the two studies. Risk of AKI in the control groups were completely different (1.2% in NAFARM 2011 versus 12.3% in POISE-2 2013).

We graded the evidence about increase in post-operative SCr as low certainty. The certainty of evidence was downgraded because of inconsistency (heterogeneity was not adequately explained by pre-specified effect modifiers) and indirectness (studies had multiple exclusion criteria with the patients included in the RCTs likely to be different from those in routine care). The results of Kulik 2004 (decrease in SCr associated with naproxen for 5 days after cardiac surgery) are in stark contrast to the results of NAFARM 2011 (study stopped because of excess risk of AKI associated with a lower dose of naproxen for 5 days after cardiac surgery). There was potential for publication bias as studies were small and commercially funded. However, the Funnel Plot was symmetrical (Figure 4). For the outcome of RRT, certainty of evidence was very low. This was downgraded because of imprecision, inconsistency and publication bias. There was imprecision due to low number of events, inconsistency as the risk of RRT was completely different in the two control groups (0.3% in NAFARM 2011 *versus 2.7*% in Rafiq 2014) and publication bias as one of the two studies was small and commercially funded.

Figure 4. Funnel plot of comparison: 2.1 Mean difference in serum creatinine



We were concerned that studies with high risk of bias would underestimate the effect of NSAIDs on post-operative kidney function. However, sensitivity analysis of post-operative SCr increase showed that exclusion of studies with high risk of overall bias or attrition bias reduced the study effects (Analysis 2.2; Analysis 2.3; Analysis 2.4).

Potential biases in the review process

The review was conducted with standard Cochrane methodology. The review was completed independently by two authors, who participated in all steps of the review. This limited the risk of errors in determining study eligibility, data extraction, risk of bias assessment and data synthesis. We did not include the results of unpublished studies. Studies with both positive and negative results were identified, making the possibility of publication bias

less likely. A strength of this review is that we included studies defining AKI using the KDIGO definition KDIGO 2012.

Agreements and disagreements with other studies or reviews

Lee 2007 concluded that NSAIDs caused a clinically unimportant reduction in kidney function on the first post-operative day in patients with normal kidney function. They examined several surrogate measures for kidney function including urinary sodium and CrCl. CrCl estimations are based on steady state measurements and so are inaccurate in AKI with fluctuating creatinine levels. Lee 2007 found a reduction in CrCl of 16 mL/min (95% CI 5 to 28) in patients treated with NSAIDs. Since this review, there is now a universally agreed definition for AKI based on SCr or urine output which has been adopted by KDIGO (KDIGO 2012). The studies included in the previous review also excluded patients with co-morbidities and so these results cannot be applied to the general population undergoing surgery as many these will be older patients with co-morbidities.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence about the safety of NSAIDs used in the peri-operative period in all patients; patients with co-morbidities were excluded and NSAIDs had uncertain effects on AKI and the need for RRT. Whilst, NSAIDs may be safely used in fit, healthy patients, care should be employed in high risk patients. We were unable to identify which patients are at risk based on the results of this review and so clinical judgement should be employed based on the individual and alternative analgesic strategies may need to be employed in selected cases.

Implications for research

Our analysis was limited to small studies excluding patients with co-morbidities. Several of the studies were designed to investigate AKI as a secondary outcome and used varying definitions for AKI. The indication for NSAID was not analgesia in all of the studies and the doses varied. Several studies excluded patients if their creatinine rose post-operatively or their urine output fell. Further larger studies using the KDIGO definition for AKI including patients with co-morbidities are required to confirm our findings.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aitken 1992

Methods	• Study design: RCT • Study duration: not reported • Study follow-up: 48 h
Participants	• Country: UK • Setting: single centre • Inclusion criteria: undergoing elective upper abdominal surgery • Number: treatment group 1 (19); treatment group 2 (23); control group (21) • Mean age (years): treatment group 1 (47.2); treatment group 2 (48.6); control group (56.1) • Sex (M/F): treatment group 1 (19/10); treatment group 2 (10/13); control group (10/11) • Exclusion criteria: respiratory insufficiency hepatic or kidney impairment; abuse of alcohol or drugs
Interventions	Treatment group 1 • Ketorolac: 12.5 mg/h IM infusion for 30 min during surgery then 2.5 mg/h for 47.5 h, with normal saline injections every 4 h Treatment group 2 • Ketorolac: 10 mg every 4 h IM for 48 h, first dose during surgery Control group • Intermittent and continuous infusions of saline to match other groups
Outcomes	• Pre-operative and post-operative CrCl, urine output, sodium output, potassium output
Notes	• Funding Source: Syntex research gave financial assistance and supplied the study drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as "double-blind"; insufficient information to permit judgement

Aitken 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	67 patients were randomised, of which 63 patients were included in the patient data table. Six patients were withdrawn from the study after 24 or 48 h of treatment due to equipment failure or on patient's request. No data on randomisation of the withdrawn patients. Of remaining 61 patients there is missing data from 15 patients, probably equally distributed amongst the intervention and placebo groups.
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	High risk	A commercial funding source was used for this study

Brinkmann 1998

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 h
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: elective infrarenal aortic surgery • Number: treatment group (67); control group (64) • Mean age ± SD (years): treatment group (13 ± 2); control group (13 ± 3) • Sex (M/F): treatment group (11/2); control group (11/2) • Exclusion criteria: NSAID medication at least 7 days prior to surgery; history of significant renal disease; evidence for renal artery stenosis on preoperative aortography.
Interventions	Treatment group • Ibuprofen: 400 mg IV before skin incision Control group • Placebo: aliquot IV before skin incision
Outcomes	• CrCl, and fractional sodium excretion before surgery, 1 h after cross-clamping, 6 h after cross-clamping and 24 h after cross-clamping (on the 1st postoperative day).
Notes	• Funding Source: not reported • Furosemide was given in post-operative period in 5 patients (treatment group 3/13, control group 2/13), indication for administration unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Brinkmann 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	All intended measurements were reported at baseline, 1 and 6 hours after cross-clamping, and on the first POD
Other bias	Unclear risk	The study was conducted by the anaesthetics department of the University of Ulm. There is no mention of funding sources

Eljezi 2017

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 48 h
Participants	• Country: France • Setting: inpatient • Inclusion criteria: patients undergoing elective open heart surgery or coronary artery bypass grafting • Number: treatment group 1 (25); treatment group 2 (25); treatment group 3 (24) control group (23) • Mean age ± SD (years): treatment group 1 (63 ± 9); treatment group 2 (63. ± 7); treatment group 3 (60 ± 11); control group (58 ± 13) • Sex (M/F): treatment group 1 (23/2); treatment group 2 (22/3); treatment group 3 (24/0) control group (12/11) • Exclusion criteria: kidney insufficiency defined as a CrCl < 60 mL/min^{-1}; hepatic insufficiency; congestive heart failure with ejection fraction < 45%; history of gastric peptic ulcer or GI bleeding; DM needing insulin therapy; preoperative coagulation disorder; allergy to NSAID; pregnancy or breastfeeding
Interventions	Treatment group 1 • IV ketoprofen: 0.5 mg/kg every 6 h for 48 h Treatment group 2 • IV ketoprofen 0.25 mg/kg every 6 h for 48 h Treatment group 3 • IV ketoprofen: 0.125 mg/kg every 6 h for 48 h Control group • IV normal saline
Outcomes	• Pre-operative SCr then SCr level at POD 1 and POD 2

Eljezi 2017 *(Continued)*

	• Urine output every 4 h until 48 h post-operatively
Notes	• Only 48 h SCr and urine output results documented • 100 patients randomised, 97 patient analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Allocation was concealed in an envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study drug was prepared by an anaesthetist nurse not involved of post-operative care, under the control of the anaesthetist in charge of the patient, who opened the allocation envelope
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no incomplete data
Selective reporting (reporting bias)	High risk	Methods state 4 hourly urinary output measurements until 48 h post-operatively and SCr measurement for POD 1 and POD 2. No urinary output results documented for 0 – 44 h. SCr documented at baseline and a percentage rise at 48 h reported. No results for POD 1 reported
Other bias	Low risk	The study was conducted by the Department of Anesthesiology (Medecine Peri-Operatoire) and the Clinical Pharmacology centre (CPC-CIC) of the University Hospital of Clermont-Ferrand (CHU Clermont-Ferrand), France. The sponsorship was limited to supplies and expenses. The sponsorship included payment for employees for study design, patient's inclusion, data entry, and analysis of the data. They also provided the study drugs at no cost. They had no influence or interference after the protocol was designed

Fayaz 2004

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 h
Participants	• Country: UK • Setting: single centre • Inclusion criteria: patients undergoing coronary artery bypass graft surgery • Number: treatment group 1 (17); treatment group 2 (17); control group (20) • Mean age ± SD (years): treatment group 1 (59.4 ± 8.4); treatment group 2 (64.0 ± 8.4); control group (64.3 ± 7.9) • Sex (M/F): treatment group 1 (9/7); treatment group 2 (11/6); control group (9/9)

Fayaz 2004 *(Continued)*

	• Exclusion criteria: previous history of peptic ulcer disease or GI bleeding; hepatic and/or kidney insufficiency (SCr > 120 µmol/L); insulin-dependent DM; left ventricular ejection fraction 30%; weight > 110 kg or < 55 kg; known allergy to study drugs. • Post-operative exclusion criteria: patients with prolonged cardiopulmonary bypass (180 min), patients requiring intra-aortic balloon pump support, patients who had excessive post-operative bleeding 150 mL/h for the first 2 h, and patients with early post-operative SCr increase (20% of baseline)
Interventions	Treatment group 1 • Diclofenac: 100 mg • Paracetamol: 1 g • Suppositories were administered 2 h after surgery. Diclofenac was repeated after 18 h and paracetamol every 6 h for 24 h Treatment group 2 • Diclofenac: 100 mg, 2 and 18 h after surgery Control Group • Placebo suppositories: 2 at same time as treatment group 1
Outcomes	• SCr
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization code was computer generated by Lab View version 2"
Allocation concealment (selection bias)	Low risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drugs made up by pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	6/60 patients withdrawn. Equally distributed across study groups and similar reasons for withdrawal given. 2 patients were withdrawn before entering the study due to oliguria and an early post-operative SCr rise (> 20% from baseline)
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Hynninen 2000

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 h
Participants	• Country: Canada • Setting: inpatient • Inclusion criteria: patients undergoing coronary artery bypass graft surgery were randomised. • Number: treatment group 1 (28); treatment group 2 (28); treatment group 3 (27); control group (31) • Mean age ± SD (years): treatment group 1 (59 ± 9); treatment group 2 (60 ± 7); treatment group 3 (58 ± 9); control group (55 ± 9) • Sex (M/F): treatment group 1 (20/8); treatment group 2 (24/4); treatment group 3 (21/6); control group (28/3) • Exclusion criteria: ejection fraction < 20%; previous cardiac surgery; insulin-dependent DM; weight > 100 kg or < 60 kg; kidney insufficiency (SCr > 130 µmol/L); allergy to propofol, morphine or NSAID; active peptic ulcer disease; history of GI bleeding; age > 75 years; warfarin, dipyridamole or heparin therapy preoperatively
Interventions	Treatment group 1 • Diclofenac: 75 mg suppository twice/d after surgery Treatment group 2 • Ketoprofen: 100 mg suppository twice/d after surgery Treatment group 3 • Indomethacin: 100 mg suppository twice/d after surgery Control group • Placebo suppository twice/d after surgery
Outcomes	• Pre-operative and post-operative SCr
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Randomisation and preparation of study drug in identically shaped suppositories was done by hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation and preparation of study drug in identically shaped suppositories was done by hospital pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/114 patients withdrawn. Of these six patients, 1 patient was withdrawn after one dose of indomethacin because of SCr increase > 20% post-operatively. This patient did not receive further NSAIDs as per protocol and was not includ-

Hynninen 2000 *(Continued)*

		ed in the post-operative outcome table. This event was mentioned in the discussion of the paper. The plausible effect size of this one event is probably not enough to have a clinically relevant impact on observed effect size
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Immer 2003

Methods	• Study design: parallel RCT • Study duration: June 2000 to October 2000 • Study follow-up: until hospital discharge
Participants	• Country: Switzerland • Setting: single centre • Inclusion criteria: patients undergoing coronary artery bypass operation • Number: treatment group 1 (20); treatment group 2 (20); control group (20) • Mean age ± SD (years): treatment group 1 (56.6 ± 8.8); treatment group 2 (60.5 ± 6.1); control group (60.5 ± 8.5) • Sex (M/F): treatment group 1 (3/17); treatment group 2 (3/17); control group (5/15) • Exclusion criteria: > 70 years; left ventricular ejection fraction < 30%; previous history of peptic ulcer disease or GI bleeding; hepatic or kidney insufficiency; known allergy to tramadol or NSAIDs and pre-operative analgesic treatment • Post-operative period exclusion criteria: delayed transfer to the general ward; SCr more than 150 µmol/L, and altered mental status
Interventions	Treatment group 1 • Diclofenac: 50 mg every 8 h orally on POD 2 and 3 Treatment group 2 • Etodolac: 300 mg every 8 h orally on POD 2 and 3 Control group • Tramadol: slow-release (150 mg every 12 h orally)
Outcomes	• Pre-operative and post-operative SCr
Notes	• Tramadol group (weak opioid) not included in analysis • POD 1 SCr data not included as study drugs were not given • CrCl measured on POD 4 • Funding Source: Study drugs were supplied by Grunenthal, Novartis Pharma and Sigma-Tau, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Immer 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	9 out of 69 patients were excluded post-operatively, prior to randomisation. One of these patients was withdrawn due to a post-operative SCr rise (> 150 µmol/L)
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	High risk	A commercial funding source was used for this study

Irwin 1995

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 48 h post-operatively
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: males undergoing elective minor orthopaedic surgery • Number: treatment group (11); control group (10) • Mean age ± SD (years): treatment group (45.6±19.0); control group (33.5±9.5) • Sex (M/F): not reported • Exclusion criteria: patients with respiratory, cardiac, hepatic or kidney insufficiency; history of peptic ulcer disease or allergy to aspirin, diclofenac or other prostaglandin inhibiting compounds
Interventions	Treatment group • Diclofenac: 100 mg suppository before surgery then 100 mg at 8am on day 1 Control group • Placebo: suppository before surgery and at 8am on day 1
Outcomes	• Pre-operative and post-operative (at 24 h and 48 h) measurements of CrCl, urine output, sodium output, potassium output, fractional excretion of sodium, fractional excretion of potassium
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Irwin 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew from study; reason for missing outcome data unlikely to be related to outcome
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Jones 2000

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 96 h post-operatively
Participants	• Country: Australia • Setting: single centre • Inclusion criteria: women aged 50 to 70 years undergoing major gynaecological surgery (ovarian, uterine or cervical cancer) • Number: treatment group (15); control group (15) • Mean age ± SD (years): treatment group (60.3 ± 6.3); control group (60.3 ± 6.9) • Sex (M/F): All female • Exclusion criteria: kidney or hepatic impairment; bleeding diathesis; hypersensitivity to NSAIDs; asthma; medications known to interfere with tenoxicam disposition
Interventions	Treatment group • Tenoxicam: 20 mg IV given 2 h before surgery Control group • Normal saline: IV given 2 h before surgery
Outcomes	• Pre-operative and post-operative (at 2, 24, 48, 72, and 96 h) measurements of CrCl, SCr, fractional excretion of sodium and potassium
Notes	• Funding source: unknown quantity of support provided by Hoffmann-La Roche & Co, Basle, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement

Jones 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	Roche pharmaceuticals coded and allocated 30 patients using random number tables
Allocation concealment (selection bias)	Low risk	Study drugs made up by Roche pharmaceuticals
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The allocation was not released until the end of clinical data collection
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The allocation was not released until the end of clinical data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	High risk	A commercial funding source was used for this study

Khalil 2006a

Methods	• Study design: RCT • Study duration: 2 years • Study follow-up: 48 hours
Participants	• Country: UK • Setting: single centre • Inclusion criteria: elective coronary artery bypass grafting • Number: treatment group (21); control group (19) • Mean age ± SD (years): treatment group (56.7 ± 9.1); control group (58.8 ± 6.6) • Sex (M/F): not reported • Exclusion criteria: diabetics; on anticoagulants; previous cerebrovascular disease
Interventions	Treatment group • Parecoxib: single IV dose of 40 mg given at closure of sternotomy Control group • Placebo: single IV dose given at closure of sternotomy
Outcomes	• 24 hour urinary CrCl, urinary a-1-microglobulin
Notes	• Funding: Pharmacia • Furosemide given in post-operative phase for oliguria; (treatment 12/21 patients, control 9/19 patients)
Risk of bias	

Khalil 2006a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation using a number generator
Allocation concealment (selection bias)	Low risk	A third party placed the results of the randomisation in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Envelopes were opened at close of the surgery and a third party prepared the study medication (placebo or treatment) which looked identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Initial power calculations resulted in an intended study population size of 60 patients. Following a global announcement of Pfizer that parecoxib was 'contraindicated in patients with ischaemic heart disease' further inclusion in the study was terminated at 40. Data of all 40 patients is presented
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	High risk	Commercial funding source Pharmacia, which is the manufacturer of Parecoxib

Koppert 2006

Methods	• Study design: parallel RCT • Study duration: 2002 to 2003 • Study follow-up: 3 POD
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: elderly patients ≥ 85 years undergoing hip replacement or surgery of the femoral shaft • Number: treatment group 1 (25); treatment group 2 (25); control group (25) • Mean age ± SD (years): treatment group 1 (76.0 ± 8.0); treatment group 2 (76.7 ± 8.9); control group (76.7 ± 8.6) • Sex (M/F): treatment group 1 (9/16); treatment group 2 (14/11); control group (11/14) • Exclusion criteria: angina or congestive heart failure; recent history of MI, coronary angioplasty, coronary arterial bypass, stroke or transient ischaemic attack; uncontrolled hypertension or uncontrolled DM; kidney disease; bleeding disorders; any disease that the investigator believed would pose a risk to the patient
Interventions	Treatment group 1 • Parecoxib: 40 mg and 12 hourly subsequently Treatment group 2 • IV paracetamol: infusion of 1000 mg and 6 hourly subsequently Control group

Koppert 2006 *(Continued)*

	• IV saline: over 10 min
Outcomes	• Differences in CrCl pre-operatively and up to 6 h post-operatively
Notes	• Funding source: unknown quantity of support provided by Bristol-Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	All study medication solutions were prepared by a hospital pharmacist who was not involved in the data collection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The anaesthesiologist, nursing staff, and the investigators were all blinded to the treatment. At the surgical ward, patients and nursing staff were unblinded to the medication.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight of 83 patients withdrew from study. Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	High risk	A commercial funding source was used for this study

Kostamovaara 1996

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 2 POD
Participants	• Country: Finland • Setting: single centre • Inclusion criteria: patients undergoing total hip (62) or knee (14) replacement • Number: treatment group 1 (19); treatment group 2 (20); treatment group 3 (18) control group (19) • Mean age ± SD (years): treatment group 1 (61 ± 10); treatment group 2 (58 ± 8); treatment group 3 (64 ± 5) control group (61 ± 7) • Sex (M/F): treatment group 1 (5/14); treatment group 2 (10/10); Treatment group 3 (15/3); control group (6/13) • Exclusion criteria: hepatic, kidney or cardiac failure; bleeding or coagulation disorders; peptic ulcer; asthma; hypersensitivity to aspirin or other NSAIDs; on cytostatic treatment
Interventions	Treatment group 1 • Ketoprofen: 50 mg IV loading dose for 30 min, followed 50 mg infusion over following 11.5 h

Kostamovaara 1996 *(Continued)*

	Treatment group 2 • Ketoprofen: 100 mg IV loading dose for 30 min, followed 100 mg infusion over following 11.5 h Treatment group 3 • Ketoprofen: 150 mg IV loading dose for 30 min, followed 150 mg infusion over following 11.5 h Control group • Isotonic saline: IV infusion for 30 min, followed by saline over following 11.5 h
Outcomes	• Pre-operative and day 2 SCr
Notes	• Funding source: Grant awarded by the Professor Arno Hollmen Fund, Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three of 76 patients withdrawn from study; reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Non-profit organisation funding received

Kulik 2004

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 4 POD
Participants	• Country: Canada • Setting: single centre • Inclusion criteria: patients undergoing elective coronary artery bypass graft • Number: treatment group (50); control group (48) • Mean age ± SE (years): treatment group (58.9 ± 1.5); control group (60.8 ± 1.4) • Sex (M/F): treatment group (46/4); control group (45/3)

Kulik 2004 *(Continued)*

	• Exclusion criteria: left ventricle ejection fraction < 20%; SCr > 130 µmol/L; preoperative use of H2 antagonists, proton pump inhibitors, steroids, NSAIDs (with exception of aspirin), narcotics or illicit drugs; history of peptic ulcer, liver disease or NSAID allergy
Interventions	Treatment group • Naproxen: 500 mg rectal suppository within 1 h after arrival in the recovery room, then every 12 h for a total of 5 doses; followed by 250 mg orally 3 times/d for 2 days Control group • Placebo: suppositories and tablets administered in a similar way as the treatment group
Outcomes	• Pre-operative and post-operative SCr, inotropic use for kidney dysfunction
Notes	• 16 patients withdrawn: 7 did not receive naproxen because of prolonged cardiopulmonary bypass time, perioperative stroke, anorexia and protocol violations; 9 did not receive placebo because of cardiac arrest, perioperative MI, elevated baseline SCr, excessive chest tube output and protocol violations • Funding source: no funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Medication was prepared by hospital pharmacy and appeared identical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication administration and data collection were done in a double blinded fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication administration and data collection were done in a double blinded fashion
Incomplete outcome data (attrition bias) All outcomes	High risk	16 of 98 patients withdrawn from the study, of these one patient had a baseline creatinine of 115 µmol/L pre-operatively. Remainder of the reasons for missing outcome data unlikely to be related to true outcome Despite 16 patients did not receive the intervention as allocated on randomisation - post-operative results of all 98 patients presented. The plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

Laisalmi 2001a

Methods	• Study design: parallel RCT

Laisalmi 2001a *(Continued)*

	• Study duration: not reported • Study follow-up: 2 POD
Participants	• Country: Finland • Setting: single centre • Inclusion criteria: ASA physical status I-II women scheduled to undergo elective breast surgery • Number: treatment group (15); control group (15) • Mean age ± SD (years): treatment group (49 ± 7); control group (45 ± 9) • Sex (M/F): all female • Exclusion criteria: patients with abnormal kidney or hepatic function
Interventions	Treatment group • 30 mg ketorolac: 30 mg IM with the premedication, "at the end of," and 6 h after anaesthesia Control group • Saline: 3 IM injections
Outcomes	• Kidney function was assessed using sensitive markers that monitor the function of different entities of the kidney at after 2h of anaesthesia, 2 and 12h after the end of anaesthesia, as well as on the first and on the second POD: U-NAG/creat for proximal tubular function, PuO2 is a marker of medullary homeostasis, and EPO that of the tubulointerstitium • The traditional function markers such as SCr and urea were also measured at 12 h after the end of anaesthesia, and on the first and second POD • Urine output
Notes	• Funding Source: Helsinki University Central Hospital EVO Grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Non-profit organisation funding received

McCrory 2002

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: until 72 h post follow-up from ICU

Participants	• Country: Ireland
	• Setting: single centre
	• Inclusion criteria: elective thoracic surgery via thoracotomy
	• Number
	  * Spinal: treatment group 1 (10); treatment group 2 (10); control group (10)
	  * Epidural: treatment group 1 (5); treatment group 2 (5); control group (5)
	• Mean age ± SD (years)
	  * Spinal: treatment group 1 (64 ± 4), treatment group 2 (63 ± 2), control (62 ± 2)
	  * Epidural: treatment group 1 (58 ± 6), treatment group 2 (56 ± 8), control (66 ± 3)
	• Sex (M/F)
	  * Spinal: treatment group 1 (6/4); treatment group 2 (5/5); control group (6/4)
	  * Epidural: treatment group 1 (3/2); treatment group 2 (3/2); control group (3/2)
	• Exclusion criteria: history of peptic ulcer disease; renal and hepatic dysfunction; psychiatric illness; any chronic pain syndrome; and consumption of NSAIDs, corticosteroids, or any other drug known to interfere with prostaglandin production for 14 days before surgery.

Interventions	Two types of administration - spinal and epidural. Each were assigned to following 3 groups Treatment group 1 • Nimesulide: 100 mg twice daily Treatment group 2 • Ibuprofen: 400 mg 4 times daily Control group • No NSAIDs or placebo
Outcomes	• 24 h urinary creatinine
Notes	• Funding Source: Baggott Street Hospital Academic Research Grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Anaesthetists and patients did have knowledge of the study and allocated treatment group. This knowledge is unlikely to influence the primary renal outcome; 24 hour urinary creatinine

McCrory 2002 *(Continued)*

		Nursing staff was unaware of patients participating in the study and will therefore not impact on the pain score outcomes presented
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Study conducted in a university teaching hospital, non-profit academic research grand received

NAFARM 2011

Methods	• Study design: parallel RCT • Study duration: 2005 to 2009 • Study follow-up: until hospital discharge
Participants	• Country: Brazil • Setting: single centre • Inclusion criteria: patients undergoing coronary artery bypass graft surgery • Number: treatment group (82); control group (79) • Mean age ± SD (years): treatment group (59.7 ± 9.8); control group (58.0 ± 8.6) • Sex (M/F): treatment group (50/32); control group (52/27) • Exclusion criteria: allergies to study medication; pregnant; off-pump surgery; history of GI bleeding; chronic liver disease; kidney insufficiency (SCr > 132.6 mol/L); thrombocytopenia; reported preoperative use of glucocorticoids; previous diagnosis of atrial fibrillation
Interventions	Treatment group • Naproxen: 275 mg twice/d for 5 days from the moment the patients returned to the ICU post surgery Control group • Placebo: twice/d for 5 days from the moment the patients returned to the ICU post surgery
Outcomes	• Kidney failure (SCr elevation ≥ 50% from baseline) • Death • Length of hospital stay
Notes	• Funding source: no funding received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The pharmacist made the randomization list and allocated the placebo and naproxen pills without the knowledge of any other person"
Allocation concealment (selection bias)	Low risk	Sealed envelope, medication appears identical, nursing staff giving out drugs are not part of the investigation team

NAFARM 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sealed envelope, medication appears identical, nursing staff giving out drugs are not part of the investigation team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sealed envelope, medication appears identical, nursing staff giving out drugs are not part of the investigation team
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results of all 161 randomised patients reported for primary and secondary outcomes
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

Ott 2003

Methods	• Study design: parallel RCT • Study duration: January and May 2000 • Study follow-up:14 POD
Participants	• Countries: USA, Canada, Germany, UK • Setting: multicentre (58) • Inclusion criteria: patients undergoing coronary artery bypass graft surgery. • Number: treatment group (311); control group (151) • Mean age ± SD (years): treatment group (60.3 ± 8.2); control group (61.3 ± 8.0) • Sex (M/F): treatment group (265/46); control group (135/16) • Exclusion criteria: patients undergoing emergency surgery and those with a recent (48 h) MI; insulin-dependent or uncontrolled diabetes; increased concentrations of liver enzymes SCr > 1.5 mg/dL (or 133 µmol/L); any coagulopathy; stroke or transient ischaemic attack within 6 months; substance abuse (opioids, any other analgesics, or alcohol); allergy to NSAIDs; history of gastric or duodenal ulcer; intra-operative complications
Interventions	Treatment group • Parecoxib: 40 mg IV was administered within 30 min after extubation and every 12 h for a minimum of 3 days. Subsequently, oral valdecoxib at a dose of 40 mg every 12 h was initiated and administered for a combined total of 14 days Control group • IV placebo: administered within 30 min after extubation and every 12 h for a minimum of 3 days. Subsequently, oral placebo every 12 h was initiated and administered for a combined total of 14 days
Outcomes	• SCr • Clinical adverse outcomes
Notes	• A typing error was found in the presentation of results on page 1485 (an increase in creatinine of 0.7 mg/dL is equivalent to 62 µmol/L, instead of 0.62 µmol/L as quoted in the text). • Note: creatinine rise as cause for withdrawal was 1.9% vs 1.3% in treatment vs placebo group • Funding source: not reported

Ott 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	After randomisation and the administration of at least one dose of the study drug, 26% of the 462 patients (equally distributed between groups) were withdrawn from the study. Most frequent reason for withdrawal was an adverse event (15.6%) of which 1.3% in the control group and 1.9% in the NSAID group were due to rise in creatinine. Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Perttunen 1992

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up:72 h post-operatively
Participants	• Country: Finland • Setting: single centre • Inclusion criteria: patients undergoing thoracoscopy • Number: treatment group (15); control group (15) • Mean age, range (years): treatment group (59.1, 38 to 75); control group (55.3, 23 to 74) • Sex (M/F): treatment group 1 (11/4); control group (13/2) • Exclusion criteria: > 75 years; cardiac, kidney or hepatic failure; history of GI bleeding or peptic ulceration; haemorrhagic diathesis and asthma; allergy to aspirin, NSAIDs or morphine; confusion; preoperative FEV1 < 60% of reference value; sleep apnoea
Interventions	Treatment group • Diclofenac: 400 mg in 400 mL NaCl 0.9%; 25 mL bolus given immediately after surgery then 2 mg/kg/24 h for 48 h Control group • 0.9% NaCl: 400 mL; 25 mL bolus given immediately after surgery then 2 mL/kg/24 h for 48 h

Perttunen 1992 *(Continued)*

Outcomes	• Pre-operative and post-operative SCr and urine output
Notes	• Funding support: supported by the Paulo Foundation, Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication looks identical; double blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurse who made up the infusions was not involved in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing secondary outcome data from 4/30 patients; insufficient reporting of reason behind missing data to permit judgement.
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Non-profit organisation funding received

Perttunen 1999

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 2 POD
Participants	• Country: Finland • Setting: single centre • 30 patients undergoing thoracoscopy • Number: treatment group 1 (10); treatment group 2 (10); control group (10) • Mean age, range (years): treatment group 1 (50.3, 26 to 70); treatment group 2 (40.6, 18 to 64); control group (45.0, 25 to 70) • Sex (M/F): treatment group 1 (5/5); treatment group 2 (6/4); control group (5/5) • Exclusion criteria: > 75 years; cardiac, kidney or hepatic failure; history of GI bleeding or peptic ulceration; haemorrhagic diathesis and asthma; allergy to aspirin, NSAIDs or morphine; confusion, preoperative FEV1 < 60% of reference value; sleep apnoea
Interventions	Treatment group 1 • Diclofenac: bolus of 17 mg 1 h before anaesthesia; followed by a 48 h continuous infusion at 1mg/kg/24 h Treatment group 2

Perttunen 1999 *(Continued)*

	• Diclofenac: bolus of 10 mg 1 h before anaesthesia, followed by a 48 h continuous infusion at 1.2mg/kg/24 h Control group • Equivalent placebo bolus and continuous infusion
Outcomes	• Creatinine at baseline, 1 h, first POD and second POD • Urine output measurement 0-22 h and 22-46 h
Notes	• Funding Source: Helsinki University Central Hospital Research Fund and Helsinki University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Envelopes were sealed and opened by nurse who was not involved in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Envelopes were sealed and opened by recovery nurse who made up the infusions. This nurse was not involved in the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to allocation of infusions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Non-profit organisation funding received

POISE-2 2013

Methods	• Study design: parallel RCT • Study duration: January 2011 to December 2013 • Study follow-up: 30 POD
Participants	• Countries: Canada, USA, Colombia, India, Spain, Australia, South Africa, Denmark, Hong Kong, Belgium, Austria, Pakistan, Peru, Malaysia, Italy, Chile, Switzerland, France, UK, Brazil, New Zealand • Setting: multicentre (88) • Inclusion criteria: patients undergoing non-cardiac surgery • Number: treatment group 1 (3443); treatment group 2 (3453); control group 1 (3462); control group 2 (3452) • Mean age ± SD (years): treatment group 1 (69.3 ± 9.9); treatment group 2 (69.1 ± 10.0); control group 1 (69.1 ± 10.0); control group 2 (69.2 ± 9.9) • Sex (M/F): treatment group 1 (1808/1635);treatment group 2 (1846/1607); control group 1 (1861/1601); control group 2 (1823/1629)

POISE-2 2013 *(Continued)*

	• Exclusion criteria: ESKD prior to randomisation; no pre- or post-randomisation SCr measurement available
Interventions	Treatment group 1 • Aspirin: 200 mg 2 to 4 h before surgery and then 100 mg for either 7 days (for those taking long-term aspirin) or 30 days (for those not taking long-term aspirin) Treatment group 2 (not included in meta-analyses) • Oral clonidine: 0.2 mg 2 to 4 h before surgery and then a transdermal clonidine patch (which provided clonidine 0.2 mg/d) until 72 h after surgery Control group 1 • Placebo: 2 to 4 h before surgery and then placebo for up to 30 days after surgery Control group 2 (not included in meta-analyses) • Placebo: 2 to 4 h before surgery and then a transdermal placebo patch until 72 h after surgery
Outcomes	• AKI • Dialysis within 30 days
Notes	• Treatment group 2 and control group 2 not included in the meta-analyses (wrong intervention) • Funding source: funding received from the industry. Sponsors of the study had no role in the design and conduct of the study, data collection and analysis or publication. • Financial support provided from Australian National Health and Medical Research Council, the Spanish Ministry of Health and Social Policy. Study drugs were provided by Boehringer Ingelheim and Bayer Pharma AG. Boehringer Ingelheim provided an uncertain amount of funding • Up to 10% of patients included had an eGFR of 45 mL/min or less at start of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomisation
Allocation concealment (selection bias)	Low risk	Concealed allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, clinicians, data collectors, and outcome adjudicators were blinded to the allocation of each intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, clinicians, data collectors, and outcome adjudicators were blinded to the allocation of each intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% missing creatinine values were reported. Multiple imputation models were used to handle missing data, which all yielded similar results
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Contribution of funding sources unclear, however financial support provided by two large governmental non-profit organisations. The authors state that the

POISE-2 2013 *(Continued)*

	sponsors had no role in the design and conduct of the study, collection, management, analysis, review or approval of the manuscript; and decision to submit the manuscript for publication

Power 1992

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 2 POD
Participants	• Country: UK • Setting: single centre • Inclusion criteria: patients undergoing open oesophagogastrectomy for cancer • Number: treatment group 1 (10); control group (10) • Mean age, range (years): treatment group (65.2, 51 to 76); control group (69.8, 50 to 79) • Sex (M/F): treatment group (9/1); control group (8/2) • Exclusion criteria: history of peptic ulceration, asthma, previous reactions to NSAID, allergies, evidence of kidney insufficiency, diuretic therapy and recent NSAID ingestion.
Interventions	Treatment group • Diclofenac: 75 mg IM at induction then 4 doses (75 mg each) every 12 h for 48 h Control group • Placebo: at induction then 4 doses every 12 h for 48 h
Outcomes	• Pre-operative and post-operative (day of the surgery, 1 day after surgery) measurement of CrCl, SCr, urine output, sodium output, potassium output, number of patients on diuretic or dopamine to treat post-operative kidney insufficiency
Notes	• Funding source: not reported • One patient in diclofenac group withdrawn due to low urine output and was later found to have had a reduced preoperative CrCl (45 mL/min). This patient recovered after IV dopamine and frusemide administration. In this study, frusemide 10 mg IV was given if urine flow rate was < 30 mL/h for 2 consecutive periods of 1 h

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was reported as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Standardised management for intervention and anaesthetic technique and fluid therapy, however unclear how patients and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Power 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	1 out of 20 patients, randomised to the active study drug group, was withdrawn after 18 h due to oliguria and severe AKI. It is plausible that the effect is enough to induce clinically relevant bias in observed effect size
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Puolakka 2009

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 20 h post-operatively
Participants	• Country: Finland • Setting: single centre • Inclusion criteria: patients undergoing laparoscopic hysterectomy • Number: treatment group (15); control group (15) • Mean age ± SD (years): treatment group (48.5 ± 7.9); control group (50.5 ± 4.5) • Sex (M/F): All female • Exclusion criteria: allergy to aspirin-like drugs or sulphonamide; bronchial asthma; liver or kidney disturbances; peptic ulcer; bleeding disorder; pregnancy; substance abuse; chronic pain
Interventions	Treatment group • Parecoxib: single dose of 80 mg IV, before the induction of anaesthesia Control group • Saline
Outcomes	• SCr and sensitive urine and serum markers for renal tubular injury directly after induction of anaesthesia, 2 h after induction, first and second POD
Notes	• Post hoc analysis shows that study is underpowered to detect statistically significant serious adverse events • Funding source: supported by the Medical Research Fund of Tampere University Hospital, Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Random numbers in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Nurse not involved in the study made up the study drugs

Puolakka 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients withdrawn. Missing data from 2 patients at variable time points. Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	Non-profit organisation funding received

Rafiq 2014

Methods	• Study design: parallel RCT • Study duration: March 2007 to August 2009 • Study follow-up: 30 POD
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: patients requiring cardiac surgery (medial sternotomy) • Number: treatment group (77); control group (74) • Mean age ± SD (years): treatment group (62 ± 12); control group (64 ± 13) • Sex (M/F): treatment group (61/16); control group (59/15) • Exclusion criteria; peripheral neuropathy; neurological disease; psychiatric illness; history of GI bleeding; chronic pain; SCr >150 µmol/L, hepatic disease with elevated liver enzymes; allergic to study medication; alcohol abuse; abuse of narcotics or medication; pregnancy; participation in other clinical trials; insufficient language skills; ICU stay > 24 h
Interventions	Treatment group • Ketorolac: 30 mg IV during extubation, followed by ibuprofen 400 mg 4 times/d Control group • Morphine: 10 mg 4 times/d.
Outcomes	• Maximum post-operative SCr and individual rise in SCr • Length of hospital stay, death and need for RRT post-operatively
Notes	• Funding source: no funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque sealed envelope

Rafiq 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 180 randomised patients, 29 patients were withdrawn prior to administration of the study drug. Missing outcome data balanced in numbers across intervention group with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Maximum SCr reported
Other bias	Low risk	The study appears to be free of other sources of bias

Rapanos 1999

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 h post-operatively
Participants	• Country: Canada • Setting: single centre • Inclusion criteria: adults undergoing elective aortocoronary bypass surgery • Number: treatment group (31); control group (26) • Median age ± SD (years): treatment group (62.2 ± 9.5); control group (59.4 ± 9.4) • Sex (M/F): treatment group (25/6); control group (20/6) • Exclusion criteria: previous history of peptic ulcer or GI bleeding; hepatic or kidney insufficiency; insulin dependent DM; known allergy to aspirin or NSAIDs; use of aspirin in the 5 days prior to surgery; gastro-epiploic artery conduit; weight < 60 kg; inability to operate patient controlled analgesia device
Interventions	Treatment group • Indomethacin: 100 mg suppository 2 to 3 h after surgery and again 12 h later Control group • Placebo: suppository 2 to 3 h after surgery and again 12 h later
Outcomes	• Pre-operative and post-operative SCr
Notes	• Funding source: Technilab Inc. supplied study drugs, without any financial support • 125 patients were consented and enrolled in the study preoperatively. Fifty-five patients were excluded post-operatively due to excessive blood loss. A further 10 patients were excluded due to protocol violations • A very healthy subgroup was studied

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rapanos 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation carried out by pharmacy department
Allocation concealment (selection bias)	Low risk	Sequential selection of previously randomised envelopes; envelopes containing study drug or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs and placebo suppositories in envelopes appearing similar
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study drugs and placebo suppositories in envelopes appearing similar
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

Slaven 1998

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 h
Participants	• Country: New Zealand • Setting: single centre • Inclusion criteria: healthy as judged by medical history, physical examination, routine biochemical and haematological screening and were rated as American Society of Anaesthesiologists (ASA) classification undergoing elective lower back surgery (laminectomies) • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (39.6 ± 14.1); control group (38.3 ± 7.2) • Sex (M/F): treatment group (10/0); control group (6/4) • Exclusion criteria: not reported
Interventions	Treatment group • Tenoxicam: 40 mg IV prior to induction Control group • Placebo: IV prior to induction
Outcomes	• Urinary CrCl, osmolar clearance and free water clearance
Notes	• Funding source: tenoxicam-placebo gift from Roche Products New Zealand Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement

Slaven 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation performed by pharmacist, randomisation technique unknown
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active agent and placebo drugs were delivered to the theatre room in prefilled syringes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Low risk	The tenocixam-placebo was a gift from Roche Products New Zealand (the manufacturer). The study design and analysis of the results were independent of any pharmaceutical company involvement.

Turner 1994

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 3 POD
Participants	• Country: Australia • Setting: single centre • Inclusion criteria: patients undergoing elective open cholecystectomy • Number: treatment group (24); control group (24) • Mean age ± SD (years): treatment group (56.5 ± 16.6); control group (49.0 ± 15.3) • Sex (M/F): treatment group (8/16); control group (10/14) • Exclusion criteria: history of peptic ulceration; bleeding disorder; kidney impairment; haemorrhoids
Interventions	Treatment group • Indomethacin suppositories: 200 mg at end of surgery then 100 mg twice daily for 3 days Control group • Placebo suppositories: according to same treatment regimen.
Outcomes	• Pre-operative and post-operative (48 h) SCr was measured in 19/50 patients
Notes	• No pre-operative and post-operative SCr measures given, rather the mean change was given for each group • Funding Source: not reported

Risk of bias

Turner 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Sequential selection of previously randomised envelopes, study drugs appearing identical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, nursing staff and medical staff were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, nursing staff and medical staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	50 patients were included in the study, 2 patients were withdrawn due to protocol violation. Of the remaining 48 patients kidney outcome data was available from 38 patients (11% missing data). No reasons for missing data was provided
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Varrassi 1994

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 h post-operatively
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: patients undergoing elective cholecystectomy • Number: treatment group (48); control group (47) • Mean age ± SE (years): treatment group (52.5 ± 1.4); control group (50.2 ± 1.6) • Sex (M/F): treatment group (17/31); control group (15/32) • Exclusion criteria: pregnancy; history of peptic ulceration; coagulopathies; impaired kidney function; allergy or intolerance to NSAIDs; alcohol or opioid abuse; children; > 65 years
Interventions	Treatment group • Ketorolac: 30 mg IM before surgery then 2 mg/h IV infusion for 24 h Control group • Normal saline: 1 mL IM then 2 mL/h IV infusion for 24 h
Outcomes	• Post-operative SCr
Notes	• Funding Source: supported in part by CNR Grants • SCr level taken in recovery (and after first IM injection of ketorolac/placebo) is used as baseline SCr level. No pre-operative SCr reported

Varrassi 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 out of 100 patients were withdrawn from the study after randomisation and administration of the study drug. Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol matches outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

AKI - acute kidney injury; ASA - American Society of Anesthesiologists; CrCl - creatinine clearance; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; GI - gastrointestinal; ICU - intensive care unit; IM - intramuscular; IV - intravenous; MI - myocardial infarction; NSAIDs - nonsteroidal anti-inflammatory drugs; POD - post-operative day/s; RRT - renal replacement therapy; SCr - serum creatinine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Castiglione 1997	Wrong control group: control group also received ketorolac
Cheruku 2004	Wrong population: patients included with a SCr up to 2.0 mg/dL Insufficient post-operative outcome measures reported; kidney function given for 3/100 patients only; all of those had a SCr above 2.0 mg/dL
Chow 2001	Wrong population: one third of patients underwent a nephrectomy; patients were excluded when a significant SCr rise was noted
Daniels 2014	Abstract-only publication; no kidney function outcome measures documented
Doyle 1998	Wrong control group: patients randomised to 2 analgesic regimens
Fredman 1999	No relevant post-operative kidney outcome measures
Grimsby 2012	Wrong population: patients with CKD were included and 111/128 patients underwent a nephrectomy

Study	Reason for exclusion
Hynes 2006	No relevant post-operative kidney outcome measures
Leeson 2007	Kidney function parameters not clearly defined
Ma 2015	No kidney function parameters documented
Merry 2002	Wrong population: patients with CKD included
Nussmeier 2005	Included 6 (1%) of patients with kidney insufficiency. Post-operative kidney failure or dysfunction reported at any time during the 30 days after surgery. No data given for the first 2 days after surgery
Nussmeier 2006	Patients were included when kidney disease was deemed significant by the investigator; 6 patients had kidney insufficiency (unknown eGFR) on randomisation. Adverse events were recorded. No SCr or urine output individually reported
Nuutinen 1991	No concise kidney outcome measures reported
Parker 1994	No concise kidney outcome measures reported
Rao 2000	Ambiguity regarding inclusion criteria. Patients excluded when 'significant renal disease' was present. No concise kidney outcomes documented; 1 patient developed transient kidney failure
Ready 1994	No concise kidney outcome measures reported
Southworth 2009	No concise kidney outcome measures reported
Varrassi 1999	No concise kidney outcomes measures reported; comment made that there was not statistically significant difference between treatment groups

CKD - chronic kidney disease; CrCl - creatinine clearance; eGFR - estimated glomerular filtration rate; SCr - serum creatinine

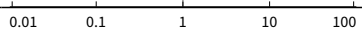
DATA AND ANALYSES

Comparison 1. Acute kidney injury

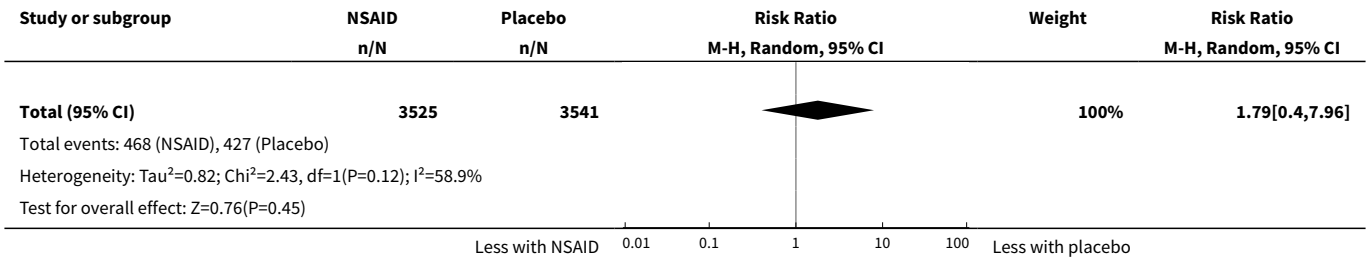
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AKI	2	7066	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.40, 7.96]

Analysis 1.1. Comparison 1 Acute kidney injury, Outcome 1 AKI.

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
NAFARM 2011	6/82	1/79		29.59%	5.78[0.71,46.94]
POISE-2 2013	462/3443	426/3462		70.41%	1.09[0.96,1.23]



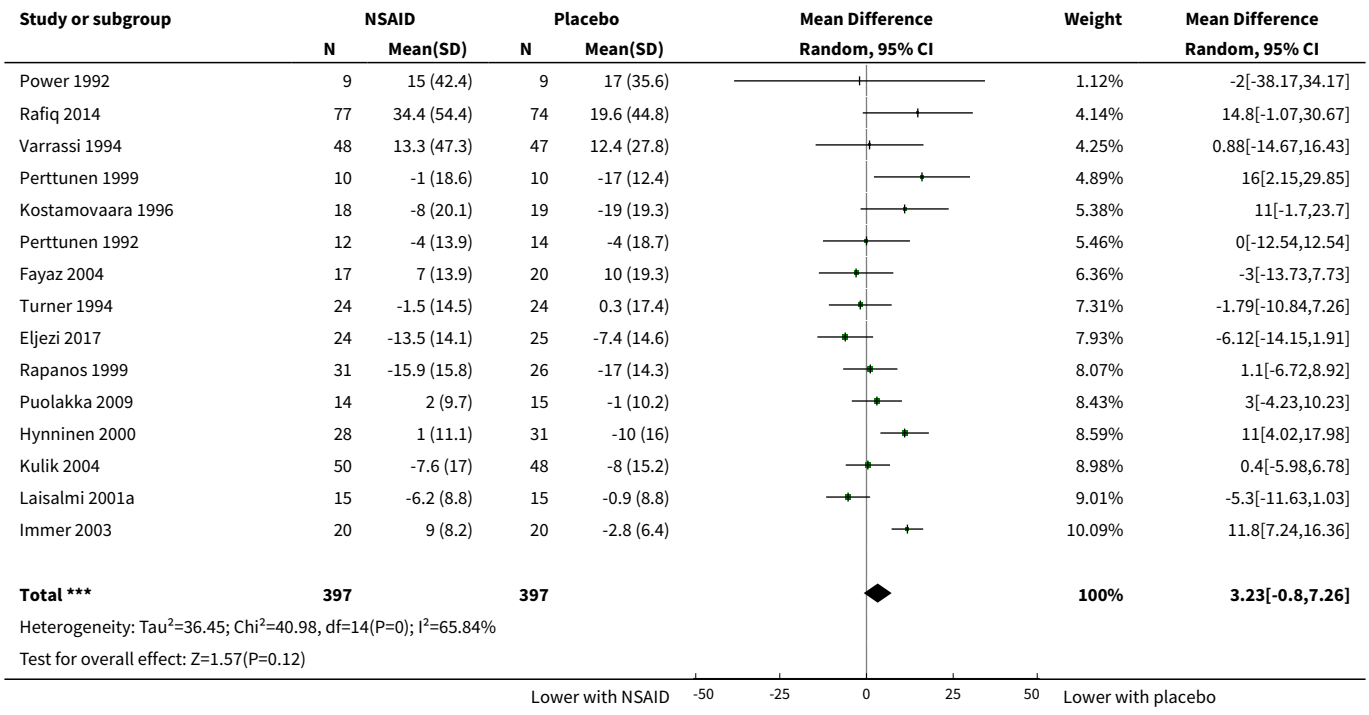
Less with NSAID | Less with placebo



Comparison 2. Serum creatinine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine (all studies)	15	794	Mean Difference (IV, Random, 95% CI)	3.23 [-0.80, 7.26]
2 Serum creatinine (excluding high risk of bias)	7	429	Mean Difference (IV, Random, 95% CI)	2.64 [-1.28, 6.55]
3 Serum creatinine (excluding high attrition bias)	11	601	Mean Difference (IV, Random, 95% CI)	2.96 [-1.57, 7.49]
4 Serum creatinine (excluding high risk of bias or high attrition bias)	6	331	Mean Difference (IV, Random, 95% CI)	3.57 [-1.35, 8.48]

Analysis 2.1. Comparison 2 Serum creatinine, Outcome 1 Serum creatinine (all studies).

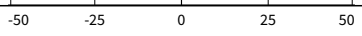


Analysis 2.2. Comparison 2 Serum creatinine, Outcome 2 Serum creatinine (excluding high risk of bias).

Study or subgroup	NSAID N	NSAID Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rafiq 2014	77	34.4 (54.4)	74	19.6 (44.8)		5.59%	14.8[-1.07,30.67]
Perttunen 1999	10	-1 (18.6)	10	-17 (12.4)		7.17%	16[2.15,29.85]
Perttunen 1992	12	-4 (13.9)	14	-4 (18.7)		8.56%	0[-12.54,12.54]
Turner 1994	24	-1.5 (14.5)	24	0.3 (17.4)		14.79%	-1.79[-10.84,7.26]
Rapanos 1999	31	-15.9 (15.8)	26	-17 (14.3)		18.53%	1.1[-6.72,8.92]
Puolakka 2009	14	2 (9.7)	15	-1 (10.2)		20.74%	3[-4.23,10.23]
Kulik 2004	50	-7.6 (17)	48	-8 (15.2)		24.61%	0.4[-5.98,6.78]
Total * **	**218**		**211**			**100%**	**2.64[-1.28,6.55]**

Heterogeneity: Tau²=5.57; Chi²=7.52, df=6(P=0.28); I²=20.23%

Test for overall effect: Z=1.32(P=0.19)

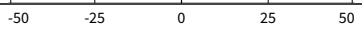


Analysis 2.3. Comparison 2 Serum creatinine, Outcome 3 Serum creatinine (excluding high attrition bias).

Study or subgroup	NSAID N	NSAID Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rafiq 2014	77	34.4 (54.4)	74	19.6 (44.8)		5.46%	14.8[-1.07,30.67]
Varrassi 1994	48	13.3 (47.3)	47	12.4 (27.8)		5.61%	0.88[-14.67,16.43]
Perttunen 1999	10	-1 (18.6)	10	-17 (12.4)		6.5%	16[2.15,29.85]
Kostamovaara 1996	18	-8 (20.1)	19	-19 (19.3)		7.19%	11[-1.7,23.7]
Perttunen 1992	12	-4 (13.9)	14	-4 (18.7)		7.3%	0[-12.54,12.54]
Turner 1994	24	-1.5 (14.5)	24	0.3 (17.4)		9.96%	-1.79[-10.84,7.26]
Eljezi 2017	24	-13.5 (14.1)	25	-7.4 (14.6)		10.88%	-6.12[-14.15,1.91]
Rapanos 1999	31	-15.9 (15.8)	26	-17 (14.3)		11.08%	1.1[-6.72,8.92]
Puolakka 2009	14	2 (9.7)	15	-1 (10.2)		11.63%	3[-4.23,10.23]
Hynninen 2000	28	1 (11.1)	31	-10 (16)		11.87%	11[4.02,17.98]
Laisalmi 2001a	15	-6.2 (8.8)	15	-0.9 (8.8)		12.5%	-5.3[-11.63,1.03]
Total * **	**301**		**300**			**100%**	**2.96[-1.57,7.49]**

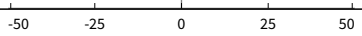
Heterogeneity: Tau²=32.36; Chi²=24.69, df=10(P=0.01); I²=59.5%

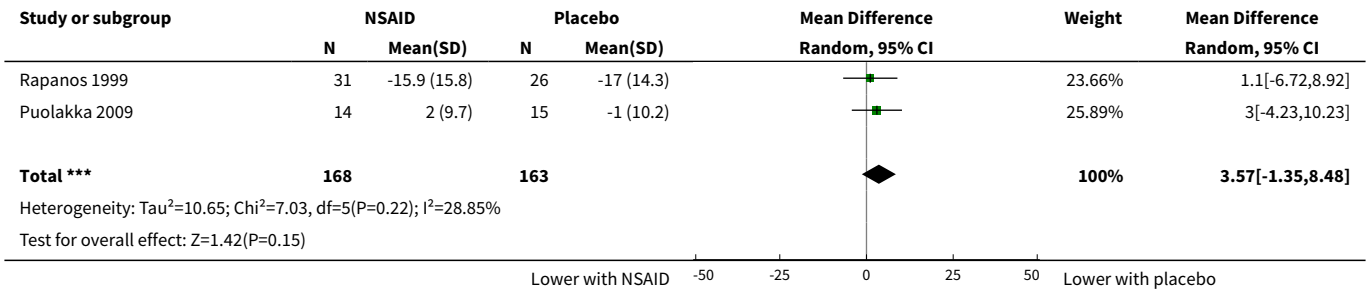
Test for overall effect: Z=1.28(P=0.2)



Analysis 2.4. Comparison 2 Serum creatinine, Outcome 4 Serum creatinine (excluding high risk of bias or high attrition bias).

Study or subgroup	NSAID N	NSAID Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rafiq 2014	77	34.4 (54.4)	74	19.6 (44.8)		8.24%	14.8[-1.07,30.67]
Perttunen 1999	10	-1 (18.6)	10	-17 (12.4)		10.37%	16[2.15,29.85]
Perttunen 1992	12	-4 (13.9)	14	-4 (18.7)		12.19%	0[-12.54,12.54]
Turner 1994	24	-1.5 (14.5)	24	0.3 (17.4)		19.64%	-1.79[-10.84,7.26]

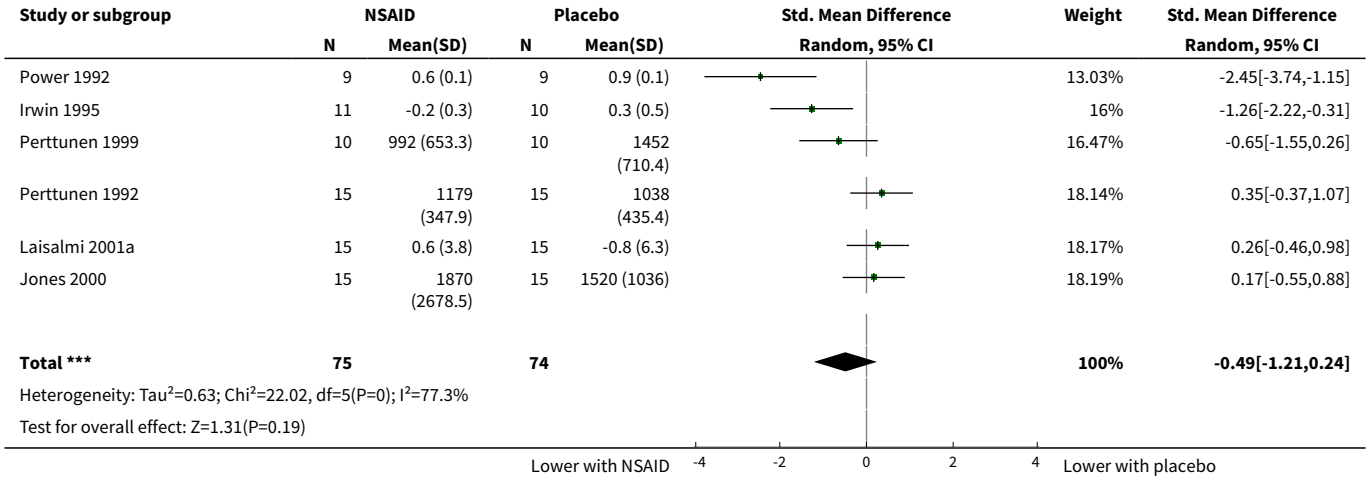




Comparison 3. Urine output

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urine output	6	149	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.21, 0.24]

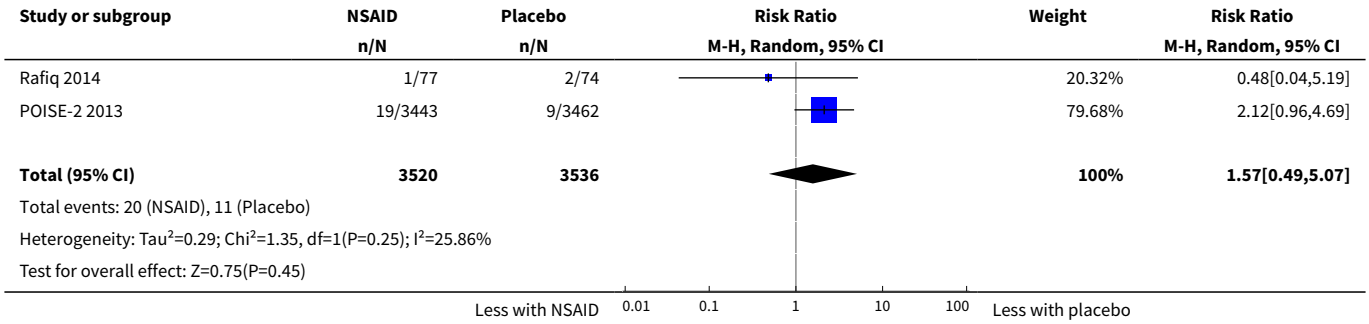
Analysis 3.1. Comparison 3 Urine output, Outcome 1 Urine output.



Comparison 4. Need for renal replacement therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 RRT	2	7056	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.49, 5.07]

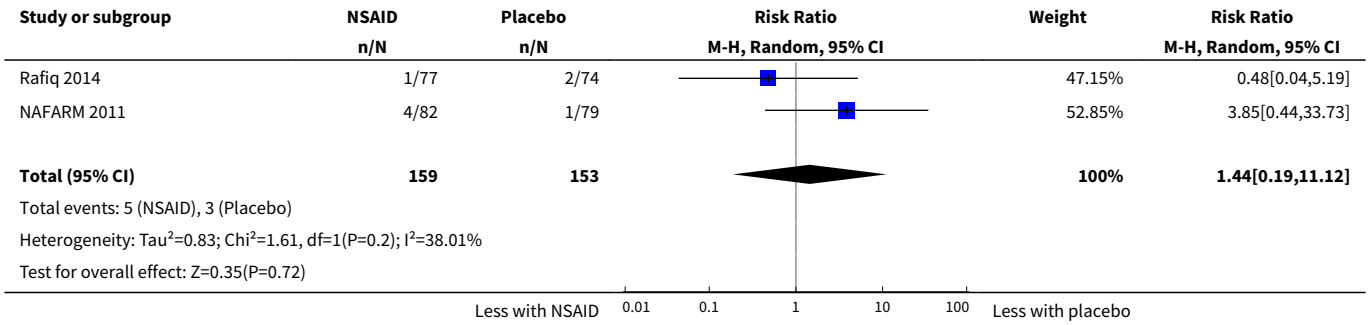
Analysis 4.1. Comparison 4 Need for renal replacement therapy, Outcome 1 RRT.



Comparison 5. Death due to any cause

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death due to any cause	2	312	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.19, 11.12]

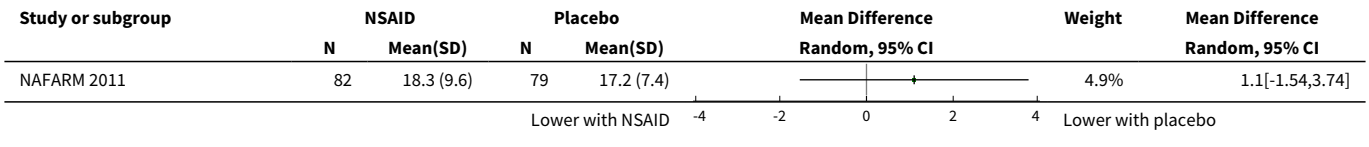
Analysis 5.1. Comparison 5 Death due to any cause, Outcome 1 Death due to any cause.

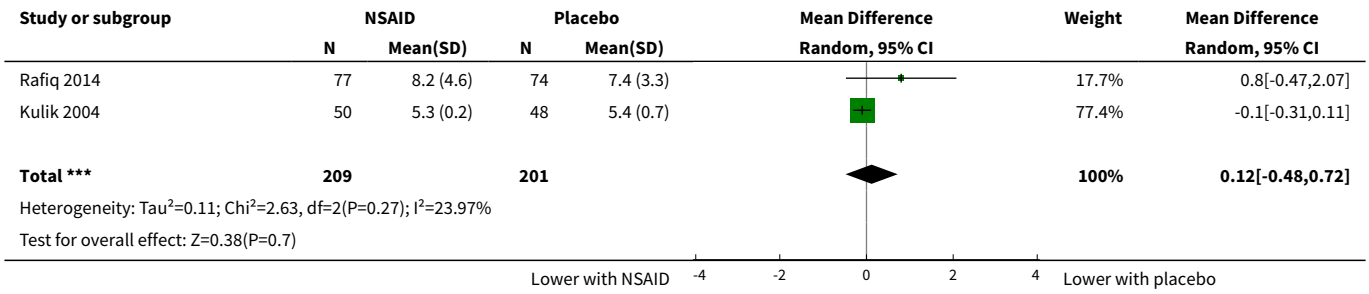


Comparison 6. Length of hospital stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay	3	410	Mean Difference (IV, Random, 95% CI)	0.12 [-0.48, 0.72]

Analysis 6.1. Comparison 6 Length of hospital stay, Outcome 1 Length of hospital stay.





ADDITIONAL TABLES

Table 1. Effect modifiers for meta-regression of change in post-operative serum creatinine

Study ID	Cardiac surgery	NSAIDs > 24 hours	Age exclusion
Eljezi 2017	Yes	Yes	> 75 years
Fayaz 2004	Yes	No	None reported
Hynninen 2000	Yes	No	> 75 years
Immer 2003	Yes	Yes, 3 days	> 70 years
Kostamovaara 1996	No, hip or knee replacement	No	None reported
Kulik 2004	Yes	Yes, 5 days	None reported
Laisalmi 2001a	No, breast surgery	No	None reported
Perttunen 1992	No, thoracoscopy	Yes, 2 days	> 75 years
Perttunen 1999	No, thoracoscopy	Yes, 2 days	> 75 years
Power 1992	No, oesophagogastrectomy	Yes, 2 days	None reported
Puolakka 2009	No, laparoscopic hysterectomy	No	None reported
Rafiq 2014	Yes	Yes, 4 days	None reported
Rapanos 1999	Yes	No	None reported
Turner 1994	No, cholecystectomy	Yes, 3 days	None reported
Varrassi 1994	No, cholecystectomy	No	> 65 years

NSAIDs - nonsteroidal anti-inflammatory drugs

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 2. ((non-steroidal next anti-inflammatory) next (agent* or drug*)):ti,ab,kw 3. ((nonsteroidal next anti-inflammatory) next (agent* or drug*)):ti,ab,kw 4. ((non-steroidal next antiinflammatory) next (agent* or drug*)):ti,ab,kw 5. ((nonsteroidal next antiinflammatory) next (agent* or drug*)):ti,ab,kw 6. NSAID*:ti,ab,kw 7. ((cox 2 inhibitor*) or (cox-2 inhibitor*)):ti,ab,kw 8. (cyclooxygenase near/2 Inhibitor*):ti,ab,kw 9. apazone:ti,ab,kw 10.aspirin:ti,ab,kw 11.clonixin:ti,ab,kw 12.diclofenac:ti,ab,kw 13.diflunisal:ti,ab,kw 14.epirizole:ti,ab,kw 15.fenoprofen:ti,ab,kw 16.feprazone:ti,ab,kw 17.flurbiprofen:ti,ab,kw 18.ibuprofen:ti,ab,kw 19.indomethacin:ti,ab,kw 20.ketoprofen:ti,ab,kw 21.ketorolac:ti,ab,kw 22.meclofenamic acid:ti,ab,kw 23.mefenamic acid:ti,ab,kw 24.naproxen:ti,ab,kw 25.niflumic acid:ti,ab,kw 26.phenylbutazone:ti,ab,kw 27.piroxicam:ti,ab,kw 28.salicylates:ti,ab,kw 29.sulindac:ti,ab,kw 30.tolmetin:ti,ab,kw 31.celecoxib:ti,ab,kw 32.etodolac:ti,ab,kw 33.meloxicam:ti,ab,kw 34.parecoxib:ti,ab,kw 35.rofecoxib:ti,ab,kw 36.tenoxicam:ti,ab,kw 37.valdecoxib:ti,ab,kw 38.{or #1-#37} 39.analgesi*:ti,ab,kw 40.an*esthesia:ti,ab,kw 41.pain:ti,ab,kw 42.(peri-operativ* or perioperativ*):ti,ab,kw 43.(postoperativ* or post-operativ*):ti,ab,kw 44.(preoperativ* or pre-operativ*):ti,ab,kw 45.{or #39-#44}

(Continued)

46.kidney:ti,ab,kw
47.renal:ti,ab,kw
48.creatinine:ti,ab,kw
49.nephrotoxi*:ti,ab,kw
50.azot*emia:ti,ab,kw
51.dialysis:ti,ab,kw
52.(hemodia* or haemodia* or hemofiltr* or haemofiltr*):ti,ab,kw
53.("glomerular filtration rate" or "glomerulus filtration rate"):ti,ab,kw
54.(gfr or egfr):ti,ab,kw
55.(urin* near/2 (volume or output)):ti,ab,kw
56.{or #46-#55}
57.{and #38, #45, #56}
58.MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees and with qualifier(s): [Adverse effects - AE]
59.{and #45, #58}
60.{or #57, #59}

MEDLINE

1. exp Anti-Inflammatory Agents, Non-Steroidal/
2. (non-steroidal anti-inflammatory adj (agent* or drug*)).tw.
3. (nonsteroidal anti-inflammatory adj (agent* or drug*)).tw.
4. (non-steroidal antiinflammatory adj (agent* or drug*)).tw.
5. (nonsteroidal antiinflammatory adj (agent* or drug*)).tw.
6. NSAID*.tw.
7. cox 2 inhibitor*.tw.
8. (cyclooxygenase adj2 Inhibitor*).tw.
9. apazone.tw.
10. aspirin.tw.
11. clonixin.tw.
12. diclofenac.tw.
13. diflunisal.tw.
14. epirizole.tw.
15. fenoprofen.tw.
16. feprazone.tw.
17. flurbiprofen.tw.
18. ibuprofen.tw.
19. indomethacin.tw.
20. ketoprofen.tw.
21. ketorolac.tw.
22. meclofenamic acid.tw.
23. mefenamic acid.tw.
24. naproxen.tw.
25. niflumic acid.tw.
26. phenylbutazone.tw.
27. piroxicam.tw.
28. salicylates.tw.
29. sulindac.tw.
30. tolmetin.tw.
31. celecoxib.tw.
32. etodolac.tw.
33. tenoxicam.tw.
34. parecoxib.tw.
35. rofecoxib.tw.

(Continued)

	36.meloxicam.tw. 37.valdecoxib.tw. 38.or/1-37 39.exp Analgesia/ 40.analgesi*.tw. 41.an?esthesia.tw. 42.Pain/ 43.Acute Pain/ 44.Pain, Postoperative/ 45.Pain Management/ 46.Perioperative Period/ 47.Postoperative Period/ 48.(peri-operative or perioperative).tw. 49.(postoperative or post-operative).tw. 50.Preoperative Period/ 51.(preoperative or pre-operative).tw. 52.Postoperative Complications/ 53.pain.tw. 54.or/39-53 55.and/38,54 56.Kidney/ 57.Kidney Diseases/ 58.Renal Insufficiency/ 59.exp Acute Kidney Injury/ 60.Creatinine/ 61.Kidney Function Tests/ 62.(kidney* or renal).tw. 63.creatinine.tw. 64.(nephrotox*).tw. 65.azot?emia.tw. 66.Renal Replacement Therapy/ 67.exp Renal Dialysis/ 68.dialysis.tw. 69.(hemodia* or haemodia* or hemofiltr* or haemofiltr*).tw. 70.glomerular filtration rate.tw. 71.(gfr or egfr).tw. 72.(urin* adj2 (volume or output)).tw. 73.or/56-72 74.and/55,73 75.exp Anti-Inflammatory Agents, Non-Steroidal/ae 76.and/54,75 77.or/74,76
EMBASE	1. exp nonsteroid antiinflammatory agent/ 2. (non-steroidal anti-inflammatory adj (agent* or drug*)).tw. 3. (nonsteroidal anti-inflammatory adj (agent* or drug*)).tw. 4. (non-steroidal antiinflammatory adj (agent* or drug*)).tw. 5. (nonsteroidal antiinflammatory adj (agent* or drug*)).tw. 6. NSAID*.tw. 7. exp Cyclooxygenase 2 Inhibitor/ 8. cox 2 inhibitor*.tw. 9. (cyclooxygenase adj2 Inhibitor*).tw.

(Continued)

10.apazone.tw.
11.aspirin.tw.
12.clonixin.tw.
13.diclofenac.tw.
14.diflunisal.tw.
15.epirizole.tw.
16.fenoprofen.tw.
17.feprazone.tw.
18.flurbiprofen.tw.
19.ibuprofen.tw.
20.indomethacin.tw.
21.ketoprofen.tw.
22.ketorolac.tw.
23.meclofenamic acid.tw.
24.mefenamic acid.tw.
25.naproxen.tw.
26.niflumic acid.tw.
27.phenylbutazone.tw.
28.piroxicam.tw.
29.salicylates.tw.
30.sulindac.tw.
31.tolmetin.tw.
32.celecoxib.tw.
33.etodolac.tw.
34.tenoxicam.tw.
35.parecoxib.tw.
36.rofecoxib.tw.
37.meloxicam.tw.
38.valdecoxib.tw.
39.or/1-38
40.exp Analgesia/
41.analgesi*.tw.
42.an?esthesia.tw.
43.Pain/
44.Postoperative Pain/
45.Postoperative Period/
46.Postoperative Analgesia/
47.Perioperative Period/
48.Preoperative Period/
49.Postoperative Complication/
50.(postoperative or post-operative).tw.
51.(peri-operative or perioperative).tw.
52.(preoperative or pre-operative).tw.
53.pain.tw.
54.or/40-53
55.and/39,54
56.Kidney/
57.Kidney Disease/
58.Kidney Failure/
59.Acute Kidney Failure/
60.Creatinine/

(Continued)

	61.Kidney Function/ 62.Kidney Function Test/ 63.(kidney or renal).tw. 64.creatinine.tw. 65.(nephrotox*).tw. 66.azot?emia.tw. 67.exp Renal Replacement Therapy/ 68.dialysis.tw. 69.(hemodia* or haemodia* or hemofiltr* or haemofiltr*).tw. 70.Glomerulus Filtration Rate/ 71.glomerular filtration rate.tw. 72.(gfr or egfr).tw. 73.Urine Volume/ 74.((urin* adj2 volume) or output).tw. 75.or/56-74 76.and/55,75 77.exp nonsteroid antiinflammatory agent/ae 78.and/54,77 79.or/76,78

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

(Continued)

interventions by participants and personnel during the study	*High risk of bias*: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

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	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Decisions based on five GRADE criteria about certainty of evidence from RCTs in Summary of Findings Table

Outcome: post-operative acute kidney injury

Criterion	Evidence	Decision
Risk of bias	NAFARM 2011 had unclear selection bias but the POISE-2 2013 was at low risk of bias	Not serious
Imprecision	7066 participants and 897 events	Serious: POISE-2 2013 had few events while NAFARM 2011 was stopped early
Inconsistency	$Chi^2 = 2.43$, df = 1 (P = 0.12); $I^2 = 59\%$	Serious: the risk of AKI in the control groups was completely different: 1.2% in NAFARM 2011 *versus* 12.3% in POISE-2 2013
Indirectness	The indications for NSAID were prevention of AKI (POISE-2 2013) or atrial fibrillation (NAFARM 2011) rather than analgesia	Serious because the doses for these indications were lower than the doses that would be used for analgesia in routine care
Publication bias	Large studies, not commercially sponsored other than supply of intervention drugs and placebo	Not serious

Outcome: difference in increase in post-operative serum creatinine

Criterion	Evidence	Decision
Risk of bias	Eight studies had high risk of bias overall or high risk of attrition bias	Not serious: the mean difference in SCr was higher in the six studies with low or unclear risk of bias (3.45, 0.12 to 6.78) than in all 15 studies (3.23, -0.80 to 7.26)
Imprecision	794 participants	Not serious
Inconsistency	$Chi^2 = 40.98$, df = 14 (P = 0.0002); $I^2 = 66\%$	Serious: the inconsistency was not adequately explained by pre-specified effect modifiers (Table 1)
Indirectness	All of the studies had multiple exclusion criteria, including age in 6 (Table 1)	Serious: the patients in these RCTs are likely to be different from those in routine care. The results of Kulik 2004 (decrease in SCr associated with naproxen for 5 days after cardiac surgery) are in stark contrast to the results of NAFARM 2011 (trial stopped because of excess risk of acute kidney injury associated a lower dose of naproxen for 5 days after cardiac surgery)
Publication bias	None of the studies were commercially sponsored	Not serious

Outcome: renal replacement therapy

Criterion	Evidence	Decision
Risk of bias	Rafiq 2014 was at high risk of performance and detection bias	Serious
Imprecision	7056 participants, 31 events	Serious, few events
Inconsistency	$Chi^2 = 1.35$, df = 1 (P = 0.25); $I^2 = 26\%$	Serious: the risk of RRT in the control groups was completely different: 0.3% in NAFARM 2011 versus 2.7% in Rafiq 2014
Indirectness	The indications for NSAID was prevention of atrial fibrillation in the largest study (NAFARM 2011) rather than analgesia	Serious because the dose of naproxen in NAFARM 2011 was much lower than would be used for analgesia
Publication bias	None of the studies were commercially sponsored	Not serious

Outcome: death

Criterion	Evidence	Decision
Risk of bias	Rafiq 2014 was at high risk of performance and detection bias	Serious
Imprecision	312 participants, 8 events	Serious: few events
Inconsistency	$Chi^2 = 1.61$, df = 1 (P = 0.20); $I^2 = 39\%$	Serious: the relative risk of death was in opposite directions: 3.85 in NAFARM 2011 versus 0.48 in Rafiq 2014
Indirectness	The indications for NSAID was prevention of atrial fibrillation in the largest study (NAFARM 2011) rather than analgesia	Serious: the dose of naproxen in NAFARM 2011 was much lower than would be used for analgesia
Publication bias	None of the studies were commercially sponsored	Not serious

Outcome: length of hospital stay

Criterion	Evidence	Decision
Risk of bias	Rafiq 2014 was at high risk of performance and detection bias; Kulik 2004 was at high risk of attrition bias	Serious
Imprecision	410 participants	Not serious: length of stay measured in all participants

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Inconsistency	$Chi^2 = 2.63$, df = 1 (P = 0.27); $I^2 = 24\%$	Serious: mean length of stay in control groups varied from 5.4 (Kulik 2004) to 17.2 days (NAFARM 2011)
Indirectness	The indications for NSAID was prevention of atrial fibrillation in the largest study (NAFARM 2011) rather than analgesia	Serious: the dose of naproxen in NAFARM 2011 was much lower than would be used for analgesia
Publication bias	None of the studies were commercially sponsored	Not serious

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: SB
2. Study selection: SB, TR
3. Extract data from studies: SB, TR
4. Enter data into RevMan: SB
5. Carry out the analysis: SB, CM, PD
6. Interpret the analysis: SB, CM,PD
7. Draft the final review: SB, TR, CM, PD
8. Disagreement resolution: PD
9. Update the review: SB

DECLARATIONS OF INTEREST

- Samira Bell: none known
- Charis A Marwick: none known
- Trijntje Rennie: none known
- Peter Davey: none known

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External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform a search for observational studies as outlined in the protocol as we found sufficient RCTs to address the aim of the review. We included two studies that had an objective other than pain relief in this review. NAFARM 2011 studied the effects of naproxen on prevention of atrial fibrillation after coronary artery bypass grafting and the POISE-2 2013 studied adverse effects of low dose aspirin following non-cardiac surgery.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Kidney Injury [chemically induced]; Anti-Inflammatory Agents, Non-Steroidal [*adverse effects]; Creatinine [blood]; Kidney [*drug effects] [physiology]; Length of Stay; Pain, Postoperative [*drug therapy]; Perioperative Care; Randomized Controlled Trials as Topic; Renal Insufficiency [chemically induced]; Urine

MeSH check words

Adult; Humans; Male