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Interventions for protecting renal function in the perioperative period (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	9
Figure 1.	9
Figure 2.	11
Figure 3.	12
Figure 4.	18
Figure 5.	19
Figure 6.	20
Figure 7.	21
DISCUSSION	21
AUTHORS' CONCLUSIONS	24
ACKNOWLEDGEMENTS	24
REFERENCES	25
CHARACTERISTICS OF STUDIES	35
DATA AND ANALYSES	84
Analysis 1.1. Comparison 1 Dopamine and analogues versus no intervention, Outcome 1 Mortality.	85
Analysis 1.2. Comparison 1 Dopamine and analogues versus no intervention, Outcome 2 Acute renal injury.	85
Analysis 1.3. Comparison 1 Dopamine and analogues versus no intervention, Outcome 3 Urine output.	86
Analysis 1.4. Comparison 1 Dopamine and analogues versus no intervention, Outcome 4 Creatinine clearance.	87
Analysis 1.5. Comparison 1 Dopamine and analogues versus no intervention, Outcome 5 Free water clearance.	88
Analysis 1.6. Comparison 1 Dopamine and analogues versus no intervention, Outcome 6 Fractional excretion of sodium.	88
Analysis 1.7. Comparison 1 Dopamine and analogues versus no intervention, Outcome 7 Renal plasma flow (24 hours).	88
Analysis 2.1. Comparison 2 Diuretics versus no intervention, Outcome 1 Mortality.	89
Analysis 2.2. Comparison 2 Diuretics versus no intervention, Outcome 2 Acute renal injury.	90
Analysis 2.3. Comparison 2 Diuretics versus no intervention, Outcome 3 Urine output.	90
Analysis 2.4. Comparison 2 Diuretics versus no intervention, Outcome 4 Creatinine clearance.	90
Analysis 3.1. Comparison 3 Calcium channel blockers versus no intervention, Outcome 1 Mortality.	91
Analysis 3.2. Comparison 3 Calcium channel blockers versus no intervention, Outcome 2 Acute renal injury.	92
Analysis 3.3. Comparison 3 Calcium channel blockers versus no intervention, Outcome 3 Urine output.	92
Analysis 3.4. Comparison 3 Calcium channel blockers versus no intervention, Outcome 4 Creatinine clearance.	92
Analysis 3.5. Comparison 3 Calcium channel blockers versus no intervention, Outcome 5 Free water clearance.	93
Analysis 4.1. Comparison 4 ACE inhibitors versus no intervention, Outcome 1 Mortality.	93
Analysis 4.2. Comparison 4 ACE inhibitors versus no intervention, Outcome 2 Acute renal injury.	94
Analysis 4.3. Comparison 4 ACE inhibitors versus no intervention, Outcome 3 Renal plasma flow.	94
Analysis 5.1. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 1 Mortality.	95
Analysis 5.2. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 2 Acute renal injury.	95
Analysis 5.3. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 3 Urine output at 24 hours.	95
Analysis 5.4. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 4 Creatinine clearance, 24 hours.	96
Analysis 5.5. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 5 Creatinine clearance, 2 to 3 days.	96
Analysis 6.1. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 1 Mortality.	97
Analysis 6.2. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 2 Acute renal injury.	97
Analysis 6.3. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 3 Urine output, 24 hours.	97
Analysis 7.1. Comparison 7 Erythropoietin (EPO) versus control, Outcome 1 Mortality.	98
Analysis 7.2. Comparison 7 Erythropoietin (EPO) versus control, Outcome 2 Acute renal injury.	98
Analysis 7.3. Comparison 7 Erythropoietin (EPO) versus control, Outcome 3 Urine output: 24 hours.	98

Analysis 7.4. Comparison 7 Erythropoietin (EPO) versus control, Outcome 4 Urine output: 2 to 3 days.	99
Analysis 7.5. Comparison 7 Erythropoietin (EPO) versus control, Outcome 5 Urine output: 5 to 7 days.	99
Analysis 8.1. Comparison 8 Intravenous fluid versus control, Outcome 1 Mortality.	100
Analysis 8.2. Comparison 8 Intravenous fluid versus control, Outcome 2 Acute renal injury.	100
Analysis 8.3. Comparison 8 Intravenous fluid versus control, Outcome 3 Creatinine clearance.	100
Analysis 9.1. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 1 Mortality.	101
Analysis 9.2. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 2 Acute renal injury.	102
Analysis 9.3. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 3 Urine output.	103
Analysis 9.4. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 4 Creatinine clearance.	104
Analysis 9.5. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 5 Free water clearance.	105
Analysis 9.6. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 6 Fractional excretion of sodium.	106
Analysis 10.1. Comparison 10 Aortic surgery: subgroup analysis, Outcome 1 Mortality.	107
Analysis 10.2. Comparison 10 Aortic surgery: subgroup analysis, Outcome 2 Acute renal injury.	107
Analysis 10.3. Comparison 10 Aortic surgery: subgroup analysis, Outcome 3 Urine output.	108
Analysis 10.4. Comparison 10 Aortic surgery: subgroup analysis, Outcome 4 Creatinine clearance.	108
Analysis 10.5. Comparison 10 Aortic surgery: subgroup analysis, Outcome 5 Free water clearance.	109
Analysis 10.6. Comparison 10 Aortic surgery: subgroup analysis, Outcome 6 Fractional excretion of sodium.	110
Analysis 10.7. Comparison 10 Aortic surgery: subgroup analysis, Outcome 7 Renal plasma flow.	110
Analysis 11.1. Comparison 11 Biliary surgery: subgroup analysis, Outcome 1 Urine output.	111
Analysis 11.2. Comparison 11 Biliary surgery: subgroup analysis, Outcome 2 Creatinine clearance.	112
Analysis 12.1. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 1 Mortality.	113
Analysis 12.2. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 2 Acute renal injury.	113
Analysis 12.3. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 3 Urine output.	114
Analysis 12.4. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 4 Creatinine clearance. ...	114
Analysis 13.1. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 1 Reported mortality, low risk of bias studies only.	115
Analysis 13.2. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 2 Acute renal injury, requiring dialysis, low risk of bias studies only.	116
Analysis 13.3. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 3 Urine output at 24 hours, low risk of bias studies only.	116
Analysis 13.4. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 4 Creatinine clearance at 24 hours, low risk of bias studies only.	117
ADDITIONAL TABLES	117
APPENDICES	127
WHAT'S NEW	130
HISTORY	130
CONTRIBUTIONS OF AUTHORS	131
DECLARATIONS OF INTEREST	131
SOURCES OF SUPPORT	131
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	132
NOTES	132
INDEX TERMS	132

[Intervention Review]

Interventions for protecting renal function in the perioperative period

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ABSTRACT

Background

Various methods have been used to try to protect kidney function in patients undergoing surgery. These most often include pharmacological interventions such as dopamine and its analogues, diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, *N*-acetyl cysteine (NAC), atrial natriuretic peptide (ANP), sodium bicarbonate, antioxidants and erythropoietin (EPO).

Objectives

This review is aimed at determining the effectiveness of various measures advocated to protect patients' kidneys during the perioperative period.

We considered the following questions: (1) Are any specific measures known to protect kidney function during the perioperative period? (2) Of measures used to protect the kidneys during the perioperative period, does any one method appear to be more effective than the others? (3) Of measures used to protect the kidneys during the perioperative period, does any one method appear to be safer than the others?

Search methods

In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 2, 2012), MEDLINE (Ovid SP) (1966 to August 2012) and EMBASE (Ovid SP) (1988 to August 2012). We originally handsearched six journals (*Anesthesia and Analgesia*, *Anesthesiology*, *Annals of Surgery*, *British Journal of Anaesthesia*, *Journal of Thoracic and Cardiovascular Surgery*, and *Journal of Vascular Surgery*) (1985 to 2004). However, because these journals are properly indexed in MEDLINE, we decided to rely on electronic searches only without handsearching the journals from 2004 onwards.

Selection criteria

We selected all randomized controlled trials in adults undergoing surgery for which a treatment measure was used for the purpose of providing renal protection during the perioperative period.

Data collection and analysis

We selected 72 studies for inclusion in this review. Two review authors extracted data from all selected studies and entered them into RevMan 5.1; then the data were appropriately analysed. We performed subgroup analyses for type of intervention, type of

surgical procedure and pre-existing renal dysfunction. We undertook sensitivity analyses for studies with high and moderately good methodological quality.

Main results

The updated review included data from 72 studies, comprising a total of 4378 participants. Of these, 2291 received some form of treatment and 2087 acted as controls. The interventions consisted most often of different pharmaceutical agents, such as dopamine and its analogues, diuretics, calcium channel blockers, ACE inhibitors, NAC, ANP, sodium bicarbonate, antioxidants and EPO or selected hydration fluids. Some clinical heterogeneity and varying risk of bias were noted amongst the studies, although we were able to meaningfully interpret the data. Results showed significant heterogeneity and indicated that most interventions provided no benefit.

Data on perioperative mortality were reported in 41 studies and data on acute renal injury in 44 studies (all interventions combined). Because of considerable clinical heterogeneity (different clinical scenarios, as well as considerable methodological variability amongst the studies), we did not perform a meta-analysis on the combined data.

Subgroup analysis of major interventions and surgical procedures showed no significant influence of interventions on reported mortality and acute renal injury. For the subgroup of participants who had pre-existing renal damage, the risk of mortality from 10 trials (959 participants) was estimated as odds ratio (OR) 0.76, 95% confidence interval (CI) 0.38 to 1.52; the risk of acute renal injury (as reported in the trials) was estimated from 11 trials (979 participants) as OR 0.43, 95% CI 0.23 to 0.80. Subgroup analysis of studies that were rated as having low risk of bias revealed that 19 studies reported mortality numbers (1604 participants); OR was 1.01, 95% CI 0.54 to 1.90. Fifteen studies reported data on acute renal injury (criteria chosen by the individual studies; 1600 participants); OR was 1.03, 95% CI 0.54 to 1.97.

Authors' conclusions

No reliable evidence from the available literature suggests that interventions during surgery can protect the kidneys from damage. However, the criteria used to diagnose acute renal damage varied in many of the older studies selected for inclusion in this review, many of which suffered from poor methodological quality such as insufficient participant numbers and poor definitions of end points such as acute renal failure and acute renal injury. Recent methods of detecting renal damage such as the use of specific biomarkers and better defined criteria for identifying renal damage (RIFLE (risk, injury, failure, loss of kidney function and end-stage renal failure) or AKI (acute kidney injury)) may have to be explored further to determine any possible benefit derived from interventions used to protect the kidneys during the perioperative period.

PLAIN LANGUAGE SUMMARY

No evidence indicates that any of the measures used to protect patients' kidneys during the perioperative period are beneficial

The kidneys may be damaged during an operation as a result of direct and indirect insult. The reasons for this are multiple and include changes to physiology brought on by the surgery and by the body's response to such insult. Damage to kidneys during the perioperative period is associated with significant morbidity and mortality. This updated Cochrane review looked at 72 randomized controlled trials (RCTs) with 4378 participants (search data until August 2012); interventions most often included pharmacological interventions (administration of dopamine and its analogues, diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, *N*-acetyl cysteine, atrial natriuretic peptide, sodium bicarbonate, antioxidants and erythropoietin) or selected hydration fluids. We attempted to identify any possible damage to the kidneys by evaluating kidney function up to seven days after the operation.

No clear evidence from available RCTs suggests that any of the measures used to protect the kidneys during the perioperative period are beneficial. These findings held true in 14 studies of patients with pre-existing renal damage and in 24 studies that were considered of good methodological quality. The primary outcomes of these studies were mortality and acute renal injury. Reported mortality in studies with low risk of bias was not different between intervention and control groups (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.52 to 1.97) or for acute renal injury (OR 1.05, 95% CI 0.55 to 2.03). The summary of findings revealed a similar picture. So we conclude that evidence suggests that none of the interventions used currently are helpful in protecting the kidneys during the perioperative period, nor do they cause increased harm.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interventions in patients with pre-existing renal dysfunction

Interventions for protecting renal function in patients with pre-existing renal impairment who are undergoing surgery

Patient or population: patients with pre-existing renal impairment

Settings: perioperative period (7 days)

Intervention: interventions to protect the kidneys during the perioperative period

Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative ef- fect (95% CI)	No. of partic- ipants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no inter- vention	Various interventions				
Mortality in patients with pre- existing renal impairment As reported in the included trials Folliow-up: 7 days	Study population		OR 0.74 (0.36 to 1.52)	959 (10 studies)	⊕⊕⊕⊕ very low a,b,c,d	Evidence is not strong and is of poor quality
	38 per 1000	29 per 1000 (15 to 56)				
	Moderate					
	20 per 1000	15 per 1000 (8 to 30)				
Acute renal injury in patients with pre-existing renal impair- ment As reported in the included trials Follow-up: 1 to 7 days	Study population		OR 0.40 (0.22 to 0.76)	979 (11 studies)	⊕⊕⊕⊕ very low e,f,g,h	Evidence is not strong and is of poor quality (al- though it might give a statistical edge)
	62 per 1000	28 per 1000 (15 to 50)				
	Moderate					
	40 per 1000	18 per 1000				

(9 to 32)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the 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; OR: Odds ratio.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

^aOnly six of the 10 studies showed low risk of bias.

^bSignificant clinical heterogeneity between studies was noted.

^cClinical heterogeneity and indications varied across the chosen studies.

^dThe numbers of events and the total numbers of cases studied were small.

^eOnly six of the 11 included studies were assessed as having low risk of bias.

^fSignificant clinical heterogeneity amongst the included studies was noted.

^gClinical scenarios in the included studies varied.

^hReported incidences were low and the numbers of participants in the included studies were small.

Summary of findings 2. Interventions to protect the kidneys in the perioperative period in patients undergoing surgery: low ROB studies only

Interventions to protect the kidneys during the perioperative period in patients undergoing surgery: low ROB studies only

Patient or population: patients undergoing surgery

Settings: perioperative period (7 days)

Intervention: interventions to protect the kidneys in patients undergoing surgery: low ROB studies only

Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Interventions to protect the kidneys:				

	low ROB cases only					
Reported mortality, low risk of bias studies only Follow-up: mean 7 days	Study population		OR 1.01 (0.52 to 1.97)	1604 (19 studies)	⊕⊕⊕⊕ very low a,b,c,d	Evidence is not strong and is of poor quality
	23 per 1000	23 per 1000 (12 to 42)				
	Moderate					
	20 per 1000	20 per 1000 (11 to 37)				
Acute renal injury, low-risk studies only	Study population		OR 1.05 (0.55 to 2.03)	1550 (16 studies)	⊕⊕⊕⊕ very low e,f,g,h	Evidence is not strong and is of poor quality (although it might give a statistical edge)
	23 per 1000	24 per 1000 (13 to 45)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the 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; **OR:** Odds ratio; **ROB:** Risk of bias.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

^aOnly six of the 10 studies showed low risk of bias.

^bSignificant clinical heterogeneity between studies was noted.

^cClinical heterogeneity and indications varied across the chosen studies.

^dThe numbers of events and the total numbers of cases studied were small.

^eOnly six of the 11 included studies were assessed as having low risk of bias.

^fSignificant clinical heterogeneity amongst the included studies was noted.

^gClinical scenarios in the included studies varied.

^hReported incidences were low and the numbers of participants in the included studies were small.

BACKGROUND

Description of the condition

Intraoperative changes in renal blood flow and glomerular filtration rate are common. Postoperative renal dysfunction is mainly attributed to adverse events that occur during the perioperative period, including hypotension, hypovolaemia and sepsis, or it may be due to perioperative administration of contrast material (Morcos 2004). The reported risk of perioperative renal failure varies according to aetiology, definition and type of surgery; acute renal failure during the perioperative period is a serious complication associated with considerable morbidity and mortality. When postoperative renal dysfunction occurs, it is generally thought to be multi-factorial in nature.

Description of the intervention

Over the past few decades, attempts have been made to protect the kidneys both during surgery and in the immediate postoperative period (Wang 2003). Various regimens, such as low-dose dopamine, dopexamine, fenoldopam or diuretics, have been tried. The results are somewhat uncertain, hence a number of other measures have been tried. These include *N*-acetyl cysteine (Adabag 2008; Barr 2008; Burns 2005; Fischer 2005; Hynninen 2006; Prasad 2010; Ristikankare 2006), atrial natriuretic peptide (ANP) (Chen 2007; Mitaka 2008; Sezai 2000; Sezai 2009) and erythropoietin (EPO) (Song 2009). Amongst nephrologists, considerable enthusiasm has surrounded the potential for EPO to provide some renal protection (Johnson 2006).

Different tests, some simple and some complicated, are used with varying success to detect acute kidney injury (AKI) in the perioperative period. Measurement of urine output over a 24-hour period after surgery is one of the simpler tests. A commonly used measure is creatinine clearance, which is often examined by using the Cockcroft-Gault formula, which takes into consideration the age, body weight and sex of the individual, as well as serum creatinine levels. Glomerular filtration rate (GFR) can be measured, as can renal plasma flow. Other tests include assessment of the ability of kidneys to clear a water load (free water clearance) and to excrete sodium (fractional excretion of sodium).

Several newer tests are used as markers of renal damage. The ratio in urine of microalbumin to creatinine (Hynninen 2006; Turner 2008) has been used but is considered an index of kidney damage, most often in chronic kidney disease. Urinary *N*-acetyl-beta-D-glucosaminidase (U-NAG) to creatinine ratio (Hynninen 2006; Mitaka 2008), retinol-binding protein (RBP) to creatinine ratio and urinary neutrophil gelatinase-associated lipocalin (NGAL) to creatinine ratio are newer methods that can be used to detect renal damage; we have looked at these tests in preparing this update of the review. Plasma cystatin C (CysC) (Chen 2007; Haase 2007; Harten 2008; Hynninen 2006) is another available marker. In a recent study (Endre 2011), glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), NGAL, CysC, kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) were used in intensive care units as biomarkers of acute kidney injury.

How the intervention might work

Over the past few decades, several strategies have been used to attempt to protect the kidneys both during surgery and in the immediate postoperative period on a physiological

basis (maintaining adequate cardiac output, maintaining renal vasodilatation, suppressing renal vasoconstriction and maintaining renal tubular flow). Various pharmacological regimens, such as use of low-dose dopamine, dopexamine, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or diuretics, have been tried. Some success has been reported with such interventions (Welch 1995) but no clear evidence of success (Renton 2005) or of deterioration in renal function has been found (Lassnigg 2000).

Dopamine, an endogenous catecholamine, given at a dose of 2 µg·kg·min to 5 µg·kg·min (low-dose or renal dopamine), causes renal vasodilatation with a dose-dependent increase in renal blood flow (McDonald 1964; Seri 1988); at higher doses, dopamine augments renal blood flow by increasing cardiac output through β-adrenergic stimulation. The effect of dopamine has been studied extensively over the years (ANZICS CTG 2000). The net sum of these actions is seen as an increase in renal blood flow, an increase in GFR, diuresis and natriuresis. Mannitol, an osmotic diuretic, attenuates ischaemic reperfusion injury through multiple mechanisms, including maintenance of glomerular filtration pressure, prevention of tubular obstruction by cellular casts, scavenging of hydroxyl free radicals and prevention of cellular swelling (Schrier 1984). Furosemide, a loop diuretic, blocks ion transport activity in the medullary thick ascending loop of Henle and enhances tubular oxygen balance by decreasing tubular oxygen demand and consumption. However, loop diuretics also cause renal cortical vasodilatation, resulting in redistribution of blood flow, which could undermine the benefit previously described (Moitra 2009). Calcium channel blockers appear to confer protection against intracellular calcium injury in ischaemic reperfusion injury (Schrier 1991). Rapid administration of fluids results in expansion of intravascular volume, leading to an increase in cardiac output. ACE inhibitors alter the balance between the vasoconstrictive and salt-retentive properties of angiotensin II and between the vasodilatory and natriuretic properties of bradykinin (Brown 1998). In the kidneys, ACE inhibitors decrease glomerular capillary pressure by decreasing arterial pressure and by selectively dilating efferent arterioles (Anderson 1986).

N-acetyl cysteine (NAC) has a variety of biological actions. It is an antioxidant (Zafarullah 2003); it stimulates endothelium-derived relaxing factor, thereby improving microvascular flow (Kiefer 2000); and it increases cyclic guanosine monophosphate (GMP) levels, thereby acting as a vasodilator and as an inhibitor of platelet aggregation. These various clinical actions might have led several investigators to focus on the use of NAC for the prevention of contrast-induced nephropathy (CIN) (Kay 2003; Tepel 2000). The natriuretic peptides play an important role in cardiovascular, renal and endocrine homeostasis. The natriuretic and diuretic actions of ANP are due to renal haemodynamic and direct tubular actions (Levin 1998). ANP increases GFR by increasing pressure within the glomerular capillaries (Marin-Grez 1986). ANP also inhibits angiotensin II—stimulated sodium and water transport in proximal tubules (Harris 1987), vasopressin-stimulated water transport in the collecting tubules (Dillingham 1986) and sodium absorption in the inner medullary collecting duct (Sonnenberg 1986). The combined effect of all of this consists of natriuresis and diuresis. Thus ANP has been used to try to counteract the two proposed pathophysiological mechanisms of decreased GFR in AKI, namely, reduced glomerular perfusion and tubular obstruction (Edelstein 1997). Accumulating evidence indicates that EPO has

tissue protective or pleiotropic effects (Chatterjee 2005; Maiese 2005) that may be useful in preventing or treating AKI. The protective mechanisms are multi-factorial and involve inhibition of apoptotic cell death, stimulation of cellular regeneration, inhibition of deleterious pathways and promotion of recovery (Moore 2011).

Why it is important to do this review

The previously published version of this review (Zacharias 2008) was unable to detect much benefit derived from various interventions to protect the kidneys during the perioperative period. The efficacy of dopamine and its analogues, diuretics, calcium channel blockers, ACE inhibitors, NAC, ANP, sodium bicarbonate, EPO and antioxidants has yet to be proved in the capacity of reversing or preventing AKI during the perioperative period. In this updated review, we are taking a fresh look at the current status of this important topic.

OBJECTIVES

This review is aimed at determining the effectiveness of various measures advocated to protect patients' kidneys during the perioperative period.

We considered the following questions: (1) Are any specific measures known to protect kidney function during the perioperative period? (2) Of measures used to protect the kidneys during the perioperative period, does any one method appear to be more effective than the others? (3) Of measures used to protect the kidneys during the perioperative period, does any one method appear to be safer than the others?

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomized controlled trials of any intervention (dopamine and its analogues, diuretics, calcium channel blockers, ACE inhibitors, *N*-acetyl cysteine, atrial natriuretic peptides, hydration fluids or any other interventions) versus control (placebo or no intervention), published in any language.

Types of participants

We included participants undergoing all types of major surgery during which a specified intervention was used to protect the kidneys from possible damage during surgery. We did not include studies that specifically considered a paediatric population. We did not include studies with participants undergoing transplant surgery (heart, liver or kidney) because of the complexity of the surgery and the postoperative management required for these participants.

Types of interventions

We included studies that used the following interventions to maintain or protect kidney function during anaesthesia and surgery.

- Dopamine and its analogues.
- Diuretics.
- Calcium channel blockers.
- Angiotensin-converting enzyme (ACE) inhibitors.

- Hydration fluids.
- *N*-acetyl cysteine.
- Atrial natriuretic peptide.
- Erythropoietin (EPO).
- Any other measures.

Types of outcome measures

Primary outcomes

Postoperative adverse outcomes. These included significant adverse outcomes: acute renal failure or death.

Secondary outcomes

Any changes in perioperative renal function. These included the following measures.

- Urine output.
- Creatinine clearance (or glomerular filtration rate).
- Renal plasma flow (or renal blood flow).
- Free water clearance.
- Fractional excretion of sodium.
- Urinary NAG/creatinine ratio.
- Urinary RBP/creatinine ratio.
- Plasma cystatin C.
- Urinary NGAL/creatinine ratio.

Search methods for identification of studies

Electronic searches

In our updated review, we searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2012); MEDLINE (Ovid SP) (1966 to August 2012); and EMBASE (Ovid SP) (1988 to August 2012). We used the search strategies given in [Appendix 1](#).

Searching other resources

We originally handsearched six major journals in anaesthesia and vascular or thoracic surgery (1985 to 2004).

- *Anesthesia and Analgesia*.
- *Anesthesiology*.
- *Annals of Surgery*.
- *British Journal of Anaesthesia*.
- *Journal of Thoracic and Cardiovascular Surgery*.
- *Journal of Vascular Surgery*.

However, because these journals are properly indexed in MEDLINE, we decided to rely on the electronic searches only without handsearching these journals from 2004 onwards.

Data collection and analysis

Selection of studies

We evaluated for appropriateness of inclusion all studies obtained by the search methods described above, as well as their abstracts and summaries. We obtained full publications for those studies, which required further assessment. Two of the review authors (MZ, NPC or PS or MM) evaluated these studies without prior consideration of the results, and consensus was reached on

the final selection. Colleagues at the local hospital or university translated some of the selected studies into English.

Data extraction and management

We used specifically designed data extractions forms to extract the relevant data ([Appendix 2](#)). Two authors (MZ, NC or PS or MM) separately extracted and compared data. We resolved differences by discussion and reaching consensus. Wherever we considered it necessary, we attempted to contact the authors for further clarification, data, or both, with limited success.

The data collected included the following.

- Reported mortality or acute renal failure.
- Nature of the surgical intervention.
- Nature of the intervention used.
- Methodological quality (risk of bias) of the study.
- Presence of pre-existing renal damage.
- Any other relevant information.

Results of the individual studies were reported in many different ways, including means, standard deviations (SDs), standard errors of the mean (SEMs), median or interquartile ranges (IQRs) or ranges. We converted standard errors of the mean and interquartile ranges to standard deviations using appropriate formulae. We considered the interquartile range to be 1.35 times the standard deviation (for the purpose of this review, we assumed that the data were normally distributed). We calculated the standard deviation as the square root of the sample size times the standard error of the mean.

We considered creatinine clearance as a surrogate measure of GFR. When data involved weights, we made an assumption of 70 kg to convert the data. When data were presented in graphical form, we extracted the numerical data from the graphs as accurately as possible. We converted all data to uniform measurements; thus urine output, creatinine clearance, renal plasma flow and free water clearance were expressed in mL/min and fractional excretion of sodium as a percentage, urinary microalbumin/creatinine ratio as mg/mg, U-NAG (*N*-acetyl-beta-D-glucosaminidase)/creatinine ratio as $\mu\text{mol}/\text{mmol}$, urinary retinol-binding protein/creatinine ratio as $\mu\text{g}/\text{mmol}$, urinary NGAL (urinary neutrophil gelatinase-associated lipocalin)/creatinine ratio as ng/mmol and plasma cystatin C as mg/L .

In this review, we chose to look at data for the various renal function tests at 24 hours, two to three days and five to seven days, because these were the times that the results were most frequently reported in the selected studies. We were reluctant to look at data collected earlier than 24 hours because these would have shown acute changes brought on by anaesthesia and surgery. Even though it is not specified in most of the publications, we assumed that data on urine output at 24 hours reflect the average reading for urine output in the first 24 hours after surgery; the same applies to urine output results at two to four days and five to seven days postoperatively. For measurements such as creatinine clearance, renal plasma flow, free water clearance and fractional excretion of sodium, we assumed that the data were obtained at the specified time.

Assessment of risk of bias in included studies

At least two review authors independently assessed each included study for methodological quality on the basis of assessment of the following domains of quality: randomization, concealment of allocation, blinding and acknowledgement of dropouts. An overall quality assessment was rated as good, moderately good or poor (see [Table 1](#)).

Measures of treatment effect

We pooled continuous outcomes with mean differences (MDs) and 95% confidence intervals (CIs). Initially, we pooled the results using a fixed-effect model, but substantial heterogeneity existed in many analyses, and we explored the reasons for this. Because of considerable heterogeneity seen in the results, we opted to present the data using a random-effects model.

Dichotomous outcomes (acute renal failure and mortality) were very rare events, hence we have presented these as odds ratios (ORs), using the Peto method.

Unit of analysis issues

We found no unit of analysis issues.

Dealing with missing data

We attempted to contact the authors of the publications to ask for information related to missing data, as well as further information on risk of bias.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots, the test for heterogeneity and I^2 . We suspected significant heterogeneity on the basis of the I^2 tests; values of I^2 greater than 25% were regarded as moderate heterogeneity and values of I^2 greater than 75% as significant heterogeneity ([Higgins 2008](#)). Clinical heterogeneity was determined on the basis of clinical and demographic data provided in the studies.

Assessment of reporting biases

Reporting biases were assessed by using funnel plots constructed from the data.

Data synthesis

We used RevMan 5.1 for the synthesis of data ([Deeks 2008](#)). Continuous data are presented as MDs with 95% CIs. Because substantial heterogeneity was suspected, these results were pooled using a random-effects model. For dichotomous outcome data (primary outcomes, mortality and acute renal injury), we used a fixed-effect model because the incidence rate was very low; results are presented as ORs, using the Peto method.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses for the following situations.

- Methods used for renal protection.
- Types of operation.
- Studies on participants with pre-existing renal dysfunction.

Sensitivity analysis

We undertook sensitivity analyses for randomized controlled trials using only studies with low or moderate risk of bias.

RESULTS

Description of studies

Details of studies can be found in '[Characteristics of included studies](#)' and '[Characteristics of excluded studies](#)'.

Results of the search

In the 2008 update ([Zacharias 2008](#)), we identified 136 studies from the MEDLINE search, 113 studies from the EMBASE search and 177 from CENTRAL (426 studies in total). We searched reference lists

and bibliographical data from all retrieved articles and reviews for additional, relevant material. We sought information from authors of published studies and contacted recognized experts on this topic about any unpublished data. We identified a further 25 studies by this method. Thus in 2008, a total of 451 studies were considered potentially eligible for this review.

The extended search strategy in 2011 yielded 655 studies, and four studies were obtained from other sources. Of these, we obtained full papers for 35 studies and included 26 additional studies in the review. A further search in August 2012 provided a further 318 studies. From this group, we added one study to the review, one conference presentation to the list of studies awaiting further analysis and one exclusion due to duplicity. In this updated review, we have included 72 studies ([Figure 1](#)).

Figure 1. Study flow diagram, as of December 2012.

Included studies

See 'Characteristics of included studies'. The 72 included studies comprised a total of 4378 participants; 2291 of these received some form of intervention to protect the kidneys, and 2087 acted as controls. Of the 72 included studies, 13 had multiple arms (Barr 2008; Berendes 1997; Carcoana 2003; Colson 1992; Costa 1990; Dehne 2001; Donmez 1998; Dural 2000; Kleinschmidt 1997; Lassnigg 2000; Wahbah 2000; Yavuz 2002B; Zanoardo 1993). We used the data from each arm separately for analysis of the interventions; whenever we did this, we adjusted (reduced) the numbers in the control groups in the appropriate sections. Barr 2008 had three arms; one arm used fenoldopam, one arm *N*-acetyl cysteine and another arm a combination of the two (the latter was excluded from the review). Berendes 1997 had three treatment arms with increasing strengths of dopexamine in cardiac surgery; another arm acted as control. We combined the three treatment groups for the purpose of analysis. Carcoana 2003 had three treatment arms and a control arm; one treatment group received dopamine infusion during the surgery, one group received a bolus of mannitol in the pump prime and the third group received both treatments. We excluded the third arm of the study. Colson 1992 had two treatment arms and one control arm; one treatment group received a calcium channel blocker, and the second group received an angiotensin-converting enzyme (ACE) inhibitor. Costa 1990 also had three arms—two treatment arms and one control arm; we excluded the arm that used multiple interventions (dopamine and SNP). Dehne 2001 had two control groups—one for participants with normal renal function and one for participants with pre-existing renal dysfunction. Intervention groups in this study (two) used dopexamine and matched the control for the presence or absence of pre-existing renal failure. Donmez 1998 used two intervention groups—one received verapamil and the other received nimodipine. Dural 2000 had three arms; one arm received dopamine, another arm received mannitol and the third arm was the control group. Kleinschmidt 1997 had two intervention groups—pentoxifylline and gamma hydroxybutyrate—and one control group. Lassnigg 2000 had three arms—two active (dopamine or furosemide) and one control. In the case of Wahbah 2000, we used only one of three treatment arms because two arms combined multiple interventions (dopamine and mannitol, or dopamine and furosemide). This study contained a fourth control arm. Yavuz 2002B had three treatment arms and one control arm; one treatment arm used two interventions simultaneously, and we excluded this arm in the appropriate sections. Zanoardo 1993 used two doses of dopamine by infusion; we combined the two groups in the analysis.

We identified three studies that were published both in abstract form and as full papers. We were unable to confirm whether they were duplicate papers and hence considered only the full papers for inclusion in the analysis (Kulka 1996; O'Hara 2002; Ryckwaert 2001) for this review. We have referred to the abstract publications (Kulka 1993; O'Hara 2002A; Ryckwaert 1995) in the table 'Characteristics of excluded studies'.

The details of participants' sex were not available for all studies, so we did not attempt to separately document this information. All included studies except one (Cregg 1999) involved adult populations; the Cregg study involved correction of scoliosis surgery and included a younger age group.

Forty-nine studies involved participants undergoing cardiac surgery (Adabag 2008; Amano 1994; Amano 1995; Ascione 1999; Barr 2008; Berendes 1997; Bergman 2002; Burns 2005; Carcoana 2003; Chen 2007; Cogliati 2007; Colson 1990; Costa 1990; Cregg 1999; Dehne 2001; Donmez 1998; Dural 2000; Durmaz 2003; Fischer 2005; Haase 2007; Haase 2009; Kaya 2007; Kleinschmidt 1997; Kramer 2002; Kulka 1996; Lassnigg 2000; Loeff 2004; Marathias 2006; Morariu 2005; Morgera 2002; Myles 1993; Nouri-Majalan 2009; Prasad 2010; Prowle 2012; Ristikankare 2006; Ryckwaert 2001; Sezai 2000; Sezai 2009; Sezai 2011; Shim 2007; Song 2009; Tang 1999; Tang 2002; Urzua 1992; Witczak 2008; Woo 2002; Yavuz 2002A; Yavuz 2002B; Zanoardo 1993). Fifteen trials included participants undergoing abdominal aortic surgery (for aortic aneurysm and occlusive arterial disease) (Colson 1992; Dawidson 1991; de Lasson 1995; de Lasson 1997; Halpenny 2002; Hynninen 2006; Lau 2001; Licker 1996; Mitaka 2008; Nicholson 1996; Pull Ter Gunne 1990; Shackford 1983; Turner 2008; Welch 1995; Wijnen 2002). Four trials consisted of participants undergoing biliary surgery (Gubern 1988; Parks 1994; Thompson 1986; Wahbah 2000); one involved laparoscopic colorectal surgery (Perez 2002); one partial nephrectomy (O'Hara 2002); and one correction of scoliosis (Cregg 1999). Fourteen studies involved participants with pre-existing renal dysfunction or those with increased risk of renal dysfunction as a result of the surgery (Adabag 2008; Burns 2005; Chen 2007; Cogliati 2007; Dehne 2001; Durmaz 2003; Haase 2007; Haase 2009; Marathias 2006; Nouri-Majalan 2009; Prasad 2010; Prowle 2012; Ristikankare 2006; Witczak 2008).

Various treatment measures were used in the different trials to protect the kidneys during the perioperative period. Interventions included dopamine and its analogue or agonist (dopexamine or fenoldopam) in 22 studies (Barr 2008; Berendes 1997; Carcoana 2003; Cogliati 2007; Costa 1990; Cregg 1999; de Lasson 1995; Dehne 2001; Dural 2000; Halpenny 2002; Lassnigg 2000; Myles 1993; O'Hara 2002; Parks 1994; Perez 2002; Tang 1999; Wahbah 2000; Welch 1995; Woo 2002; Yavuz 2002A; Yavuz 2002B; Zanoardo 1993); diuretics (mannitol, furosemide) in six trials (Carcoana 2003; Dural 2000; Gubern 1988; Lassnigg 2000; Nicholson 1996; Shim 2007); calcium channel blockers (diltiazem, nicardipine, felodipine, verapamil, nimodipine) in nine trials (Amano 1995; Bergman 2002; Cho 2009; Colson 1992; de Lasson 1997; Donmez 1998; Witczak 2008; Yavuz 2002B; Zanoardo 1993); ACE inhibitors (captopril, enalapril) in four trials (Colson 1990; Colson 1992; Licker 1996; Ryckwaert 2001); *N*-acetyl cysteine in seven trials (Adabag 2008; Barr 2008; Burns 2005; Fischer 2005; Hynninen 2006; Prasad 2010; Ristikankare 2006); atrial natriuretic peptide in five trials (Chen 2007; Mitaka 2008; Sezai 2000; Sezai 2009; Sezai 2011); and, in one trial each, glutathione (Amano 1994), prostaglandin (Morgera 2002), theophylline (Kramer 2002), clonidine (Kulka 1996), dexamethasone (Loeff 2004; Morariu 2005), pentoxifylline (Kleinschmidt 1997), gamma hydroxybutyrate (Kleinschmidt 1997), antioxidant therapy (Wijnen 2002), phenylephrine (Urzua 1992), ursodeoxycholic acid (Thompson 1986) and preoperative haemodialysis (Durmaz 2003); and surgical measures such as off-pump cardiac surgery (Ascione 1999; Tang 2002) and an extraperitoneal approach to aortic surgery (Lau 2001). Five studies looked at the effects of hydration fluids (Dawidson 1991; Harten 2008; Marathias 2006; Pull Ter Gunne 1990; Shackford 1983). One trial (Song 2009) used erythropoietin (EPO) as the intervention. We have included this because it is currently an area of interest in this field.

We have conducted subgroup analyses of trials to observe the effects of different interventions on renal protection in the perioperative period. These subgroups included dopamine and its analogue or agonist; diuretics; calcium channel blockers; ACE inhibitors; atrial natriuretic peptide; *N*-acetyl cysteine; EPO; and hydration fluids. We also undertook subgroup analyses to observe the effects of the type of surgery; these included cardiac surgery, abdominal aortic surgery and biliary surgery. We performed a limited subgroup analysis of studies with pre-existing renal impairment.

We also completed a limited sensitivity analysis on studies with low risk of bias.

Excluded studies

We provide the reasons for excluding studies in the table 'Characteristics of excluded studies'. Studies published in languages other than English (German, Turkish, Serbian, Russian and Japanese) were translated with the help of volunteers. All of these studies were available as full publications. We have had only limited success in receiving adequate information and feedback from the authors whom we attempted to contact, in spite of repeated attempts. All included and excluded studies were published between 1976 and 2012. We did not include three studies in the analysis because we could not confirm that they were not duplicate publications (see below). We did not include three studies authored by Boldt et al because of issues surrounding the reliability of studies from that group of researchers.

Risk of bias in included studies

Even though we included 72 studies in the review, the overall methodological quality of the studies was poor. We used a quality assessment system (see 'Methodological quality of studies' [Table 1](#)) based on method of randomization, allocation concealment, blinding and reporting of dropouts as the criterion. We scored the methodological quality of selected studies as good, moderately good or poor. When randomization, allocation concealment and blinding (participants, researchers, care givers and nurses) were adequately described and appropriately done, we classified the study as a good quality study. When randomization, allocation concealment and blinding (participants, researchers, care givers and nurses) were stated to have been done but no details were given in the publication, we classified the study as moderately good. When we found no evidence of allocation concealment and blinding, we classified the study as having poor methodological quality. The risk of bias information is given in [Figure 2](#) and [Figure 3](#).

The methodological quality assessment identified twelve studies of good quality ([Adabag 2008](#); [Burns 2005](#); [Carcoana 2003](#); [Cogliati 2007](#); [Fischer 2005](#); [Haase 2007](#); [Haase 2009](#); [Kaya 2007](#); [Myles 1993](#); [Prowle 2012](#); [Song 2009](#); [Turner 2008](#)) and another nine studies for which the methodological quality was considered moderately good ([Ascione 1999](#); [Barr 2008](#); [Cho 2009](#); [de Lasson 1997](#); [Hynninen 2006](#); [Lassnigg 2000](#); [Perez 2002](#); [Ristikankare 2006](#); [Shim 2007](#)). Most of the studies that we assessed (51 studies) were classified as having poor methodological quality (see 'Methodological quality of studies', additional [Table 1](#)). We had no success in obtaining data on concealment of allocation, blinding and method of randomization from most of the trial authors. Some trials were old, and we had very little chance of contacting these authors. We received replies from only five authors.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across 78 included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)
Adabag 2008	+	+	+	?
Amano 1994	-	-	-	?
Amano 1995	-	-	-	?
Ascione 1999	+	?	-	?
Barr 2008	+	?	?	+
Berendes 1997	-	-	-	?
Bergman 2002	?	-	-	+
Burns 2005	+	+	+	+
Carcoana 2003	+	?	+	+
Chen 2007	?	?	?	+
Cho 2009	+	?	-	?
Cogliati 2007	+	+	+	+
Colson 1990	?	?	?	?
Colson 1992	?	?	?	?
Costa 1990	?	-	-	?
Cregg 1999	?	-	-	?
Dawidson 1991	+	?	-	?
Dehne 2001	?	-	-	+
de Lasson 1995	?	+	-	?
de Lasson 1997	+	?	?	+
Donmez 1998	?	?	?	?
Dural 2000	?	?	-	?

Figure 3. (Continued)

Dural 2000	?	?	-	?
Durmaz 2003	-	-	-	?
Fischer 2005	+	?	+	+
Gubern 1988	?	?	?	+
Haase 2007	+	+	+	+
Haase 2009	+	+	+	+
Halpenny 2002	?	?	-	+
Harten 2008	-	?	-	+
Hynninen 2006	+	+	?	?
Kaya 2007	+	+	+	+
Kleinschmidt 1997	+	-	-	-
Kramer 2002	?	-	-	?
Kulka 1996	?	?	?	+
Lassnigg 2000	+	+	?	+
Lau 2001	?	?	-	+
Licker 1996	?	?	?	+
Loef 2004	?	-	?	+
Marathias 2006	?	-	-	-
Mitaka 2008	?	?	?	?
Morariu 2005	?	-	?	+
Morgera 2002	?	-	-	+
Myles 1993	+	+	+	+
Nicholson 1996	?	-	-	-
Nouri-Majalan 2009	?	?	?	?
O'Hara 2002	?	-	-	+
Parks 1994	?	-	-	-
Perez 2002	+	?	+	+
Prasad 2010	?	-	-	?
Prowle 2012	+	+	+	+
Pull Ter Gunne 1990	?	?	?	?
Ristikankare 2006	+	?	?	+

Figure 3. (Continued)

Ristikankare 2006	+	?	?	+
Ryckwaert 2001	?	?	+	?
Sezai 2000	?	?	+	?
Sezai 2009	?	?	-	-
Sezai 2011	?	-	?	+
Shackford 1983	?	-	?	?
Shim 2007	+	+	+	?
Song 2009	+	+	+	+
Tang 1999	?	-	-	-
Tang 2002	?	-	-	+
Thompson 1986	?	-	-	+
Turner 2008	+	+	+	+
Urzua 1992	+	-	-	+
Wahbah 2000	?	?	-	-
Welch 1995	?	-	-	-
Wijnen 2002	?	-	-	?
Witczak 2008	?	-	-	?
Woo 2002	?	-	-	+
Yavuz 2002A	?	-	-	?
Yavuz 2002B	?	-	-	?
Zanardo 1993	?	-	-	?

Allocation

See 'Characteristics of included studies' and Table 1 for details.

Blinding

See 'Characteristics of included studies' and Table 1 for details.

Incomplete outcome data

Data are available in 'Characteristics of included studies'.

Selective reporting

Funnel plots for primary outcomes, reported mortality and reported acute renal failure showed no evidence of selective reporting (see Analysis 1.1 and Analysis 1.2).

Other potential sources of bias

None of the publications mentioned any conflict of interest with respect to the choice of drugs used. The following studies

acknowledged pharmaceutical company sponsorships: de Lasson 1995; de Lasson 1997; Halpenny 2002; Kramer 2002; Lassnigg 2000; and Thompson 1986.

We constructed funnel plots to detect publication bias in primary outcomes, mortality and acute renal injury (failure) but employed this approach only in studies that looked at participants with pre-existing renal damage and studies that were assessed to have low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Interventions in patients with pre-existing renal dysfunction; **Summary of findings 2** Interventions to protect the kidneys in the perioperative period in patients undergoing surgery: low ROB studies only

We collected and analysed data from the selected 72 studies.

The dichotomous data (mortality and acute renal failure) consisted of rare events, so we used the Peto method of analysis and reported these results as Peto odds ratios (ORs) with 95% confidence intervals (CIs). We presented all continuous data results as mean differences (MDs) with 95% CIs. Results were plagued by heterogeneity throughout the analyses, so we used a random-effects model instead of a fixed-effect model. We undertook subgroup analysis for treatment measures and type of surgery. We were able to conduct only limited subgroup analysis for studies with pre-existing renal impairment because of the inadequate number of trials identified. A limited sensitivity analysis was done for studies with low risk of bias. To make the review less cumbersome for the reader, study results are listed in the text only when they were considered essential; references to appropriate 'Data and Analysis' tables are given.

Mortality

Data on perioperative mortality were reported in 41 studies, which included 3116 participants. Many cases of mortality were due to a combination of factors, including surgical causes and pathology. The risk of mortality was very low, and we did not perform a meta-analysis because of the significant clinical heterogeneity noted.

Acute renal injury

Acute renal injury (renal damage) in the postoperative period was reported in 44 studies. Many studies did not specify the criteria used to diagnose acute renal failure (ARF), hence we obtained information from these studies on the numbers of participants with acute renal injury requiring renal replacement therapy, in both treatment and control groups. Reported incidences were very low, and because of the significant clinical heterogeneity observed, we did not perform a meta-analysis of the data.

Effectiveness of measures used for renal protection

In this section, we tried to combine the data from the 72 identified studies to ascertain the effectiveness of treatments provided to protect the kidneys during the perioperative period compared with findings in the control population. Again, because of clinical heterogeneity in the form of different procedures and populations and decades of reporting such data, we decided to refrain from combining the data for a meta-analysis.

Effect of various interventions on renal protection

Most studies looked at dopamine and its analogues, although some trials used other measures to protect the kidneys during the perioperative period.

Dopamine or its analogues

Infusions of dopamine or its analogue (dopexamine) or agonist (fenoldopam) were used as treatment in 22 studies (Barr 2008; Berendes 1997; Carcoana 2003; Cogliati 2007; Costa 1990; Clegg 1999; de Lasson 1995; Dehne 2001; Dural 2000; Haase 2007; Halpenny 2002; Lassnigg 2000; Myles 1993; O'Hara 2002; Parks 1994; Perez 2002; Tang 1999; Wahbah 2000; Welch 1995; Woo 2002; Yavuz 2002A; Yavuz 2002B).

Mortality was reported in 11 trials (583 participants, OR 1.50, 95% CI 0.48 to 4.73, $I^2 = 25\%$; see Analysis 1.1), and acute renal injury was reported in 10 trials (541 participants, OR 1.36, 95% CI 0.44 to 4.23, $I^2 = 63\%$; see Analysis 1.2).

Urine output at 24 hours after operation was studied in 13 trials (see Analysis 1.3.1). Considerable heterogeneity was observed ($I^2 = 92\%$), and no difference was noted between intervention and control groups (MD 0.18 mL/min, 95% CI -0.19 to 0.54). Urine flow at two to three days showed no significant increase with the intervention in seven studies (see Analysis 1.3.2); the urine flow difference was 0.51 mL/min (95% CI 0.04 to 0.97), and heterogeneity was high ($I^2 = 95\%$). On the fifth to seventh day, treatment did not offer any advantages in five trials (see Analysis 1.3.3) (MD 0.23 mL/min, 95% CI -0.06 to 0.51, $I^2 = 72\%$).

Creatinine clearance was studied in 15 trials after dopamine or its analogues were administered (see Analysis 1.4). Fourteen trials reported creatinine clearance at 24 hours; nine studies at two to three days; and five studies at five to seven days after an operation. Analysis showed no significant difference between intervention and control groups at 24 hours (616 participants, MD 7.17 mL/min, 95% CI -5.53 to 19.86) and considerable heterogeneity ($I^2 = 91\%$); one study, in particular, favoured the treatment group (Berendes 1997). No differences were reported at two to four days (MD 7.31 mL/min, 95% CI -6.19 to 20.82, $I^2 = 94\%$) or at five to seven days after the operation (MD -3.33 mL/min, 95% CI -13.63 to 6.98, $I^2 = 18\%$).

Free water clearance in mL/min was looked at 24 hours after surgery in six trials (see Analysis 1.5). Results showed no difference between treatment and control groups (MD 0.03 mL/min, 95% CI -0.17 to 0.22, $I^2 = 0\%$). Fractional excretion of sodium at 24 hours was reported in five trials (see Analysis 1.6). As in the previous section, we did not analyse these data.

Renal blood flow in mL/min was studied at 24 hours after surgery in only two trials (see Analysis 1.7) (de Lasson 1995; O'Hara 2002). No difference was noted (48 participants, MD 75.36 mL/min, 95% CI -63.27 to 213.98, $I^2 = 45\%$).

Diuretics

Mortality was reported in four trials (255 participants, OR 2.49, 95% CI 0.50 to 7.74, $I^2 = 0\%$; see Analysis 2.1), and acute renal injury was reported in five trials (305 participants, OR 2.39, 95% CI 0.68 to 8.47, $I^2 = 35\%$; see Analysis 2.2).

Mannitol or furosemide was used as treatment in six studies. Data were available for only five studies (see Analysis 2.3). Urine output did not show a significant difference between groups at 24 hours in four studies (MD 0.10 mL/min, 95% CI -0.12 to 0.33, $I^2 = 0\%$; see Analysis 2.3.1); at two to three days in three studies (MD 0.17 mL/min, 95% CI -0.06 to 0.40, $I^2 = 0\%$). No significant differences were noted on any occasion.

Creatinine clearance was measured at 24 hours in three studies. This measure showed no statistically significant differences (see Analysis 2.4.1; MD -18.02 mL/min, 95% CI -41.78 to 5.75, $I^2 = 55\%$). The same was true on the second to fourth day (see Analysis 2.4.2; MD 2.33 mL/min, 95% CI -14.76 to 19.42, $I^2 = 0\%$).

Calcium channel blockers

Mortality was reported in two trials (68 participants), and acute renal injury was reported in six trials (172 participants, OR 0.11, 95% CI 0.01 to 1.17; see Analysis 3.1 and Analysis 3.2, respectively).

Calcium channel blockers such as diltiazem, nifedipine and felodipine were used in nine studies. Four studies looked at urine output at 24 hours after treatment; no difference was observed between treatment and control groups (MD 0.23 mL/min, 95% CI 0.02 to 0.45, $I^2 = 0\%$; see [Analysis 3.3.1](#)). Five studies looked at creatinine clearance at 24 hours postoperatively (see [Analysis 3.4.1](#)). No advantage was derived from treatment (MD 4.74 mL/min, 95% CI -3.30 to 12.77, $I^2 = 57\%$). A total of 251 participants were included in the four studies.

Three studies measured free water clearance at 24 hours (see [Analysis 3.5.1](#)) and reported no difference (MD -0.09 mL/min, 95% CI -0.47 to 0.29, $I^2 = 43\%$).

ACE inhibitors

Data were insufficient for calculations of risk of mortality and acute renal injury in this intervention group (see [Analysis 4.1](#) and [Analysis 4.2](#)).

Four trials ([Colson 1990](#); [Colson 1992](#); [Licker 1996](#); [Ryckwaert 2001](#)) looked at the usefulness of ACE inhibitors (enalapril or captopril) as renal protective agents. Data from three studies show that renal plasma flow in mL/min at the end of the operation (see [Analysis 4.3.1](#)) was not significantly different (MD 46.37 mL/min, 95% CI -68.61 to 161.34, $I^2 = 0\%$).

Atrial Natriuretic Peptide

Mortality was reported in three trials (825 participants, OR 0.52, 95% CI 0.19 to 1.44, $I^2 = 48\%$; see [Analysis 5.1](#)), and acute renal injury was reported in four trials (865 participants, OR 0.23, 95% CI 0.08 to 0.64, $I^2 = 0\%$; see [Analysis 5.2](#)).

Five trials produced evidence for the use of atrial natriuretic peptide (ANP) ([Chen 2007](#); [Mitaka 2008](#); [Sezai 2000](#); [Sezai 2009](#); [Sezai 2011](#)). Much larger numbers of participants were included in [Sezai 2009](#) and [Sezai 2011](#) (789 participants), and this considerably influenced the meta-analysis.

Urine output at 24 hours showed no significant change in three studies; this favoured the intervention (4.82 mL/min, 95% CI -2.74 to 12.38, $I^2 = 100\%$; see [Analysis 5.3](#)). Creatinine clearance at 24 hours in five studies showed similar results, favouring treatment by 4.31 mL/min (95% CI 0.34 to 8.28, $I^2 = 99\%$; see [Analysis 5.4](#)). Creatinine clearance at 2 to 3 days in four studies favoured the intervention (13.11 mL/min, 95% CI 13.11 to 13.76, but with $I^2 = 100\%$; see [Analysis 5.5](#)). The poor methodological quality and the large heterogeneity ($I^2 = 100\%$) of the two dominant studies ([Sezai 2009](#); [Sezai 2011](#)) make any conclusions worthless.

N-Acetyl Cysteine

Mortality was reported in six trials (641 participants, OR 1.01, 95% CI 0.42 to 2.42, $I^2 = 0\%$; see [Analysis 6.1](#)), and acute renal injury was reported in five trials (601 participants, OR 0.91, 95% CI 0.32 to 2.62; $I^2 = 0\%$; see [Analysis 6.2](#)).

Seven trials used administration of N-acetyl cysteine (NAC) as a measure to protect the kidneys intraoperatively ([Adabag 2008](#); [Barr 2008](#); [Burns 2005](#); [Fischer 2005](#); [Haase 2007](#); [Hynninen 2006](#); [Prasad 2010](#); [Ristikankare 2006](#)). Urine output at 24 hours was estimated in two studies (146 participants). No differences were reported (0.23 mL/min, 95% CI -0.21 to 0.68, $I^2 = 47\%$).

Erythropoietin (EPO)

Recognition of EPO as a possible drug for renal protection is increasing, hence we reported data from the single available study. One study ([Song 2009](#)) used this drug in participants undergoing cardiac surgery, some of whom had pre-existing raised creatinine. The data are given in [Analysis 7.3](#), [Analysis 7.4](#) and [Analysis 7.5](#).

We estimated the risk of mortality with this intervention in one study (71 participants, OR 0.13, 95% CI 0.00 to 6.63; see [Analysis 7.1](#)). The risk of acute renal injury was not estimable from this single intervention study (see [Analysis 7.2](#)).

Intravenous fluid

Mortality was reported in four trials (152 participants, OR 0.75, 95% CI 0.16 to 3.42, $I^2 = 0\%$; see [Analysis 8.1](#)), and acute renal injury was reported in three trials (123 participants, OR 0.22, 95% CI 0.05 to 0.96, $I^2 = 56\%$; see [Analysis 8.2](#)).

Five trials studied the role of intravenous fluids such as colloids and hypertonic saline ([Dawidson 1991](#); [Harten 2008](#); [Marathias 2006](#); [Pull Ter Gunne 1990](#); [Shackford 1983](#)). Two studies ([Pull Ter Gunne 1990](#); [Shackford 1983](#)) looked at creatinine clearance at 24 hours (see [Analysis 8.3.1](#)), and no difference was noted (MD -10.34 mL/min, 95% CI -29.57 to 8.88, $I^2 = 0\%$).

Cardiac surgery

Forty-eight studies looked at the influence of different interventions in protecting the kidneys during cardiac surgery, and various measures were attempted.

Mortality

The risk of mortality (as reported in the trials) was estimated from 26 trials (2390 participants, OR 0.96, 95% CI 0.56 to 1.64, $I^2 = 10\%$; see [Analysis 9.1](#)).

Acute renal injury

The risk of acute renal injury (as reported in the trials) was estimated from 31 trials (2504 participants, OR 0.55, 95% CI 0.32 to 0.92, $I^2 = 49\%$; see [Analysis 9.2](#)).

Urine output

Seventeen studies (774 participants in the intervention groups and 701 participants in the control groups) looked at the influence of different interventions on urine output after cardiac surgery at 24 hours (see [Analysis 9.3.1](#)). Urine output increased by 0.26 mL/min in the treatment group (95% CI 0.17 to 0.36) but with significant heterogeneity in the results ($I^2 = 86\%$). Nine studies (see [Analysis 9.3.2](#)) looked at urine output two to three days after surgery. This measurement also showed no difference between intervention and control groups (MD 0.21 mL/min, 95% CI -0.13 to 0.54, $I^2 = 100\%$).

Creatinine clearance

Twenty-four studies (see [Analysis 9.4.1](#)) looked at creatinine clearance after cardiac surgery at 24 hours in 1120 participants in the intervention groups and in 1016 participants in the control groups. The results suggested no significant improvement in creatinine clearance with treatment compared with control (MD 9.38 mL/min, 95% CI -5.99 to 24.74). Heterogeneity was high ($I^2 = 100\%$). Creatinine clearance was reported in 17 studies at two to

three days after cardiac surgery (see [Analysis 9.4.2](#)) and in seven studies on the fifth to seventh day (see [Analysis 9.4.3](#)). Any evidence of beneficial effects of treatment in the later postoperative days was not clear because of the high heterogeneity of the results. Creatinine clearance improved on the second to third postoperative days (MD 14.21 mL/min, 95% CI 3.58 to 24.85, $I^2 = 100\%$) and on the fifth to seventh postoperative days (MD 14.99 mL/min, 95% CI 0.84 to 29.13, $I^2 = 97\%$). However, it is worthwhile noting that [Sezai 2000](#), [Sezai 2009](#) and [Sezai 2011](#) (using atrial natriuretic peptide infusion as the treatment) estimated the GFR, which considerably favoured the treatment groups; the latter two studies included disproportionately high numbers of participants (789) and showed poor methodological quality.

Free water clearance

Free water clearance in mL/min was measured at 24 hours in seven studies (see [Analysis 9.5.1](#)). The results suggested less water clearance with treatment at 24 hours (MD -1.81 mL/min, 95% CI -2.02 to -1.60), with significant heterogeneity ($I^2 = 98\%$). Again, [Sezai 2009](#) has largely influenced the results. A difference was reported from the second to the third day in four studies (MD -3.55 mL/min, 95% CI -3.89 to -0.32) but with significant heterogeneity ($I^2 = 99\%$).

Fractional excretion of sodium

Eight studies documented fractional excretion of sodium at 24 hours, and three studies at two to three days postoperatively (see [Analysis 9.6](#)).

Aortic surgery

Mortality

The risk of mortality (as reported in the trials) was estimated from eight trials (236 participants, OR 0.76, 95% CI 0.20 to 2.89, $I^2 = 5\%$; see [Analysis 10.1](#)).

Acute renal injury

The risk of acute renal injury (as reported in the trials) was estimated from eight trials (284 participants, OR 0.62, 95% CI 0.11 to 3.70, $I^2 = 0\%$; see [Analysis 10.2](#)).

Urine output

Seven studies measured urine output at 24 hours after elective aortic surgery. No demonstrable benefit was derived from treatment (see [Analysis 10.3.1](#); MD -0.04 mL/min, 95% CI -0.10 to 0.19, $I^2 = 0\%$). Two trials measured urine output on second and third postoperative days and on fifth and seventh postoperative days (see [Analysis 10.3.2](#) and [Analysis 10.3.3](#)) and showed no difference with treatment (MD 0.26 mL/min, 95% CI -0.06 to 0.58, $I^2 = 12\%$ and MD -0.09 mL/min, 95% CI -0.39 to 0.21, $I^2 = 23\%$, respectively).

Creatinine clearance

Ten studies (see [Analysis 10.4](#)) looked at creatinine clearance after elective aortic surgery. All ten studies estimated creatinine clearance at 24 hours after surgery (see [Analysis 10.4.1](#)), and the results suggested no benefit resulting from treatment (MD 7.99 mL/min, 95% CI -0.77 to 16.74, $I^2 = 22\%$). The same conclusions were drawn from five trials that measured creatinine clearance on the second to third postoperative days and on the fifth to seventh postoperative days (see [Analysis 10.4.2](#) and [Analysis 10.4.3](#)). The MD

were 11.62 mL/min (95% CI -6.13 to 29.37, $I^2 = 46\%$) and -12.85 mL/min (95% CI -26.41 to 0.72, $I^2 = 5\%$), respectively. It is interesting to note that heterogeneity was moderate in these results.

Free water clearance

Five trials studied this outcome at 24 hours after aortic surgery (see [Analysis 10.5.1](#)). Results showed no significant benefit derived from treatment (MD -0.25 mL/min, 95% CI -0.51 to 0.01, $I^2 = 0\%$). Two studies looked at free water clearance on the second to fourth postoperative days and on the fifth to seventh postoperative days (see [Analysis 10.5.2](#) and [Analysis 10.5.3](#)). No differences were noted (MD 0.37 mL/min, 95% CI -0.12 to 0.85, $I^2 = 0\%$ and MD 0.24 mL/min, 95% CI -0.13 to 0.61, $I^2 = 0\%$, respectively).

Fractional excretion of sodium

Five studies reported this outcome (see [Analysis 10.6.1](#)) at 24 hours, and two studies (see [Analysis 10.6.2](#)) reported the results on the second to fourth postoperative days.

Renal plasma flow

Four trials estimated renal plasma flow after aortic surgery (see 'Data and analyses'; [Analysis 10.7](#)). Analysis of results at the end of the operation in two studies (see [Analysis 10.7.1](#)) showed no statistically significant difference between treatment and control groups (MD 50.29 mL/min, 95% CI -92.83 to 193.40, $I^2 = 28\%$). The same held true for renal plasma flow at 24 hours after operation in two studies (see [Analysis 10.7](#); MD 45.86 mL/min, 95% CI -18.64 to 110.36, $I^2 = 0\%$).

Biliary surgery

Urine output

Only two trials looked at urine output at 24 hours, two to four days, and five to seven days after biliary surgery (see [Analysis 11.1](#)). Some evidence from these two studies showed that urine output was less at 24 hours after an intervention was used (MD -0.59 mL/min, 95% CI -0.99 to -0.19, $I^2 = 18\%$), but it was not different at two to four days (MD 0.24 mL/min, 95% CI -0.22 to 0.69, $I^2 = 26\%$) and favoured control at five to seven days (MD 0.23 mL/min, 95% CI 0.09 to 0.37, $I^2 = 0\%$).

Creatinine clearance

Three trials measured creatinine clearance in mL/min at 24 hours (see [Analysis 11.2.1](#)). No benefit was derived from the use of an intervention (MD -2.84 mL/min, 95% CI -14.07 to 8.39, $I^2 = 46\%$). The same was true for creatinine clearance values from three trials measuring creatinine clearance on the second to fourth postoperative days (see [Analysis 11.2.2](#); MD 0.42 mL/min, 95% CI -16.68 to 17.52, $I^2 = 8\%$) and from two trials at five to seven days postoperatively (MD 0.58 mL/min, 95% CI -16.43 to 17.60, $I^2 = 28\%$).

Pre-existing renal impairment

Fourteen studies included participants with pre-existing renal impairment or high risk of renal damage, although different criteria were used ([Adabag 2008](#); [Burns 2005](#); [Chen 2007](#); [Cogliati 2007](#); [Dehne 2001](#); [Durmaz 2003](#); [Haase 2007](#); [Haase 2009](#); [Marathias 2006](#); [Nouri-Majalan 2009](#); [Prasad 2010](#); [Prowle 2012](#); [Ristikankare 2006](#); [Witczak 2008](#)). All of these trials involved participants undergoing cardiac surgery. [Bergman 2002](#) used

diltiazem infusions; Costa 1990 used dopamine or dopexamine infusions; Durmaz 2003 used preoperative haemodialysis; and Marathias 2006 used preoperative hydration. We identified an additional ten studies with pre-existing renal damage.

Ten studies looked at mortality. No differences were noted between treatment groups and control groups (OR 0.74, 95% CI 0.36 to 1.52,

$I^2 = 20\%$; see Analysis 12.1). Participants who developed acute renal injury requiring renal dialysis were reported in eleven studies (OR 0.40, 95% CI 0.22 to 0.76, $I^2 = 37\%$; see Analysis 12.2). Both of these analyses used the fixed-effect model because the incidence rate was very low. Studies were sufficient for the construction of funnel plots (Figure 4 and Figure 5); both suggested no significant publication bias.

Figure 4. Funnel plot of comparison: 12 Studies on participants with pre-existing renal impairment, outcome: 12.1 Mortality.

Figure 5. Funnel plot of comparison: 12 Studies on participants with pre-existing renal impairment, outcome: 12.2 Acute renal injury.

Four studies looked at urine output at 24 hours. The heterogeneity of these studies was large and hence precludes any conclusions; at 24 hours, the difference between intervention groups and control groups was 0.55 mL/min (95% CI 0.37 to 0.74 mL, $I^2 = 76\%$; see [Analysis 12.3.1](#)), and at 2 to 3 days postoperatively, the difference was 0.48 mL/min (95% CI 0.32 to 0.64, $I^2 = 98\%$; see [Analysis 12.3.2](#)). Four studies also looked at creatinine clearance at 24 hours, and the difference was insignificant (0.65 mL/min, 95% CI -0.75 to 2.06, $I^2 = 97\%$; see [Analysis 12.4.1](#)). On postoperative days 2 to 3, the difference was 1.33 mL/min in three studies (95% CI -0.02 to 2.68, $I^2 = 95\%$; see [Analysis 12.4.2](#)).

Low risk of bias studies

In this update, we identified 24 studies as having low risk of bias (Additional [Table 1, Characteristics of included studies](#)), 12 of them being assessed as good ([Adabag 2008](#); [Burns 2005](#); [Cogliati 2007](#); [Fischer 2005](#); [Haase 2007](#); [Haase 2009](#); [Kaya 2007](#); [Myles 1993](#);

[Prowle 2012](#); [Shim 2007](#); [Song 2009](#); [Turner 2008](#)) and 12 assessed as moderately good ([Ascione 1999](#); [Barr 2008](#); [Carcoana 2003](#); [Cho 2009](#); [Dawidson 1991](#); [de Lasson 1995](#); [de Lasson 1997](#); [Hynninen 2006](#); [Lassnigg 2000](#); [Morariu 2005](#); [Perez 2002](#); [Ristikankare 2006](#)). Data from these studies were subjected to sensitivity analysis. Unfortunately, reports on [Perez 2002](#) contained data that were unsuitable for analysis, and this was confirmed by contact with the authors. We performed sensitivity analyses on the low risk of bias studies, and available data enabled us to report on mortality, acute renal impairment requiring renal supportive measures (dialysis) and urine output and creatinine clearance at 24 hours.

Nineteen studies reported mortality numbers (1604 participants, OR 1.01, 95% CI 0.52 to 1.97, $I^2 = 0\%$; see [Analysis 13.1](#)). Fifteen studies reported data on acute renal injury requiring dialysis (1600 participants, OR 1.05, 95% CI 0.55 to 2.03, $I^2 = 1\%$; see [Analysis 13.2](#)). Studies were sufficient for construction of funnel plots ([Figure 6](#) and [Figure 7](#)); both suggested no significant publication bias.

Figure 6. Funnel plot of comparison: 13 Studies with low risk of bias: sensitivity analysis, outcome: 13.1 Reported mortality, low risk of bias studies only.

Figure 7. Funnel plot of comparison: 13 Studies with low risk of bias: sensitivity analysis, outcome: 13.2 Acute renal injury, requiring dialysis, low risk of bias studies only.

Urine output at 24 hours was reported in 11 studies; the difference was 0.20 mL/min (95% CI -0.04 to 0.44 mL/min, $I^2 = 71\%$; see [Analysis 13.3](#)). Creatinine clearance at 24 hours was reported in nine studies, and the difference was 6.59 mL/min (95% CI -3.53 to 16.72 mL/min, $I^2 = 94\%$; see [Analysis 13.4](#)).

Results suggested that even the low risk of bias studies, although few, showed no overall advantage for treatment versus control groups.

Assessment of small study bias

Funnel plots were examined for meta-analyses with 10 or more studies. Results showed no evidence of small sample biases (graphs not shown).

Summary of findings

A summary of findings (SoF) table was developed using GradePro on studies with pre-existing renal impairment ([Summary of findings for the main comparison](#)). The results suggest no advantage of interventions for mortality, but statistical evidence suggests that interventions might be helpful for reducing acute renal injury. However, it should be noted that the evidence is of low quality because clinical heterogeneity was considerable. Studies with low risk of bias ([Summary of findings 2](#)) show no significant changes in reported perioperative mortality and in acute renal injury between intervention and control groups. Both SoF analyses suffer from low

quality of evidence because of clinical heterogeneity and the small numbers of participants and events included in each study.

DISCUSSION

Summary of main results

Renal dysfunction after major surgery is one of the causes of postoperative morbidity and mortality. The cause of renal injury in the postoperative period is thought to be multi-factorial. Over the past three or four decades, many studies have tried to identify interventions that could provide renal protection during the perioperative period. Many different interventions have been tried, such as continuous infusions of dopamine or its analogues, use of diuretics such as mannitol and diligent use of ACE inhibitors and calcium channel blockers, to name a few. Drugs such as *N*-acetyl cysteine (NAC), atrial natriuretic peptide (ANP), sodium bicarbonate, antioxidants and erythropoietin (EPO) are some of the more recent interventions. None of these interventions appears to have a good evidence base.

We were unable to combine the whole data because of significant heterogeneity among selected studies. Given the large range of treatments, operation types and methods used to protect the kidneys, it is not surprising that heterogeneity is large. Heterogeneity could have been the result of multiple causes, including differences in the nature of treatment, the duration of treatment or participants' conditions, and of course it could have

been related to the methodological quality of the studies. We used subgroup analyses to explore this further.

We performed subgroup analyses for the different interventions that were studied. Dopamine and its analogues showed no improvement in urine output or in other tests such as creatinine clearance, free water clearance or fractional excretion of sodium. Overall, on the basis of available studies, it appears that dopamine and its analogues do not offer much protection to the kidneys. It is worth noting that in a multi-centre study of participants in intensive care units (ANZICS CTG 2000), no significant benefit of dopamine was noted for these seriously ill individuals.

A 'Summary of findings' table, which used only low risk of bias studies, showed no benefit derived from interventions for domains of mortality and acute renal injury requiring dialysis. We looked at the effects of some of the major interventions (dopamine and its analogues, diuretics, calcium channel blockers, ACE inhibitors, atrial natriuretic peptide, *N*-acetyl cysteine, IV fluids and EPO) and major surgical procedures (cardiac surgery and abdominal aortic surgery), as well as groups of participants identified as having pre-existing renal damage; none of these groups showed a significant change in reported mortality or renal injury (as reported in the individual studies) in treatment groups versus control groups.

Overall completeness and applicability of evidence

Many physiological and biochemical variables can be used as markers of change in renal function. The various trials included in this review used numerous different markers as indicators of altered renal function. Each test has significant limitations, and results of the analysis must be interpreted in the context of these limitations.

- Plasma creatinine is the most frequently measured marker of renal function. It is assumed that plasma creatinine remains constant and that clearance of creatinine occurs solely by glomerular filtration. Thus plasma creatinine is an indirect determinant of glomerular filtration rate (GFR). However, a greater than 50% reduction in GFR is needed before a change in plasma creatinine is seen. Plasma creatinine also reflects an individual's muscle mass, and alterations in muscle mass influence the plasma creatinine concentration, which does not reflect changes in GFR. A small amount of tubular excretion of creatinine occurs, which, in terms of normal GFR, is insignificant. However, with severe renal impairment, tubular secretion of creatinine has a greater role, and therefore plasma creatinine does not accurately reflect GFR. GFR is usually determined by the clearance of an inert substance, which is freely filtered at the glomerulus and has no tubular secretion or reabsorption. The gold standard has been estimation of inulin clearance. Creatinine clearance correlates well with GFR. For accuracy, it is essential that creatinine clearance is determined correctly. This requires a timed and complete collection of urine, along with a plasma creatinine determination. A variety of formulae have been derived that are based on plasma creatinine, body weight and age and are to estimate creatinine clearance and hence GFR. When renal function is stable, these estimates correlate well with measured GFR ($r = 0.9$).
- Urine output is a non-specific measure of renal function. Clearly, if no urine is produced, then no glomerular filtration occurs. However, urine output can be influenced by several factors that regulate renal tubular handling of water. Oliguria (<400 mL

urine/24 h) may just reflect excess salt and water retention by the kidney due to low fluid intake, not necessarily impaired renal function or the effects of increased antidiuretic hormone (ADH) release—a normal response to surgery or stress.

- In clinical practice, renal blood flow is rarely determined, but this can be done by using clearance techniques using the Fick principle.
- Free water clearance measures urinary concentrating ability. Any form of damage to the kidney impairs urinary concentrating ability. With renal tubular injury, free water clearance is impaired. Likewise, free water clearance is modified by diuretic therapy.
- The fractional excretion of sodium has been used as a marker of renal function. More correctly, it reflects renal tubular reabsorption of sodium. The normal physiological response to a reduction in renal perfusion and glomerular filtration is to activate the tubular glomerular feedback mechanism, leading to increased reabsorption of sodium, along with water. The net effect consists of increased blood pressure and hence renal perfusion. In the acute situation (the first 24 hours after an event that affects renal function), low fractional sodium excretion ($\text{FeNa} < 1\%$) indicates impaired renal perfusion. With any form of established renal damage, or the use of diuretics, the fractional excretion of sodium is increased and becomes impossible to interpret. It is, therefore, essential that the changes in markers of renal function that were recorded in the analysed papers are examined critically for the variables that influence reported measurements. Conclusions drawn from the results should be closely examined for the validity of the renal function measures that were used. An inability to correctly interpret the results prompted us to refrain from analysing the data on FeNa and instead to provide the raw data.
- Newer advances in determining acute renal injury have been reported. These include use of various biomarkers such as urinary *N*-acetyl-beta-D-glucosaminidase (U-NAG) to creatinine ratio, urine retinol-binding protein (RBP) to creatinine ratio and urinary neutrophil gelatinase-associated lipocalin (NGAL) to creatinine ratio and blood plasma cystatin C levels. We have looked at these tests in this review update.

We believe it is important to emphasize that the lack of statistical significance described in this review could be due to many factors. We have already discussed heterogeneity as a significant factor; causes of heterogeneity include different types and durations of operations, gender differences, smoking status, state of nutrition, age, alcohol intake and co-morbidities such as hypertension, diabetes or other unknown causes. The potential role of publication (or small sample) bias is also important. One of the common methods employed to facilitate recognition of publication bias is the funnel plot. The most common reasons for small sample bias are the reluctance of trialists or journal editors to publish because results are non—statistically significant, but other reasons include small numbers of cases investigated in trials; lack of allocation concealment; and inadequate blinding. All of these events may result in misleading positive outcomes, leading to publication bias. Apart from visual examination of funnel plots, various complicated statistical methods are available, but none are wholly satisfactory for recognizing and avoiding small sample bias. A high level of suspicion is always required when reviews consisting of poor quality studies and studies with small sample sizes are interpreted, as with this review. Of particular concern are the high I^2 values seen

in many analyses; these may be due to significant statistical and clinical heterogeneity.

Results obtained with the use of diuretics were disappointing and suggested no real advantage for participants who received the treatment. The same is true for the use of calcium channel blockers and ACE inhibitors, both of which apparently offer no advantages. The use of hydration fluids also showed no obvious advantage for clear fluids over specialized colloid solutions, although the methodology of the studies and the information provided were of poor quality. It is interesting to note that only four studies investigated the role of different types of intravenous fluids in the perioperative setting, although in most studies participants were well hydrated. [Wahbah 2000](#) makes special mention of the fluid status of participants. Is it simply that kidneys are at their happiest when they have a good pre-load to wash out toxic substances?

Other interventions such as *N*-acetyl cysteine and EPO have failed to show any advantage. It is a matter of note that a meta-analysis of studies using Atrial Natriuretic Peptides has shown some benefit of treatment in the form of improved creatinine clearance. However, caution is required in accepting these findings because two large studies conducted by one particular author reported an advantage of NAC over controls and considerably influenced the overall results ([Sezai 2009](#); [Sezai 2011](#)).

Potential renal damage in participants with pre-existing renal injury is widely recognized ([Wijeyesundera 2006](#)). One area of interest for the authors of this review involved looking at the beneficial effects of treatment in participants with pre-existing renal impairment. Fortunately, we were able to include in this updated review 14 studies that considered this topic. These studies used different interventions. Unfortunately, available data are somewhat limited for the purpose of analysis. No difference was noted in reported mortality, but some advantage seems to be associated with treatment intervention, thus avoiding acute renal injury. Note that we have previously discussed differing criteria between studies for the diagnosis of acute renal damage. Urine output seems to improve when interventions are provided for patients with pre-existing renal damage, but the heterogeneity of the studies makes the results less valid.

We performed a sensitivity analysis of 24 studies of high and moderately high methodological quality. The results suggest no benefit for mortality or acute renal damage associated with treatment intervention. A marginal advantage seen in better urine output at 24 hours was offset by high heterogeneity, and no advantage was noted for creatinine clearance at 24 hours. These results substantiate the overall findings on questionable renal protection effects for various interventions given during the perioperative period.

It is important to remember that the effect of ADH is part of the usual stress response of surgery. Both urine output and free water clearance in the first 12 to 24 hours after surgery are reduced because of the influence of ADH ([Brazel 1996](#)). Fractional excretion of sodium is increased with the use of diuretics. Hence we would question the worth of measurements of urine output, free water clearance and fractional excretion of sodium as measures of renal function in the perioperative period. Glomerular filtration rate (and creatinine clearance) and renal plasma flow are good measures of renal function, but these must be measured accurately if meaningful conclusions are to be drawn.

Quality of the evidence

A major outcome of interest, mortality, was reported in a number of studies. Only a small number of deaths were reported in the trials, and this review shows that no advantage was conferred by individual interventions. Similarly, another outcome of major importance, acute renal injury after operation, was reported in only a few of the included studies. No evidence suggests that specific interventions offered any advantages for participants. However, it is important to recognize that the methodological quality of many of the included studies was poor and that the number of reported cases was small. Another point to consider is the inconsistency of the criteria used to diagnose renal injury across multiple studies. As a result, the statistical significance may not indicate a true advantage of interventions over no interventions.

In the subgroup of surgical procedures, cardiac surgery, aortic surgery and biliary surgery were considered for analysis. In cardiac surgery, interventions helped to increase urine output at 24 hours after surgery, but a high level of heterogeneity made the results unconvincing. Creatinine clearance also improved slightly at two to three days and five to seven days after surgery with treatment given to participants undergoing cardiac surgery, but the results are considerably swayed by the studies conducted by Sezai et al ([Sezai 2009](#); [Sezai 2011](#)). None of the other tests showed any significant changes. Reported mortality and acute renal injury were no different after cardiac surgery and after abdominal aortic surgery.

No benefit was noted in other forms of interventions and surgery. However, the number and quality of studies in these areas are limited.

Potential biases in the review process

Even though we included 72 studies in this review, the overall methodological quality of the studies was poor. The methodological quality assessment identified twelve studies of good quality and another nine studies in which the methodological quality was considered moderately good. Most of the studies that we assessed (51 studies) were classified as showing poor methodological quality. This would reflect on any conclusions drawn from this review.

A note of caution: Many of the studies included in this review are old and were conducted before adaptations were made to the RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) classification, which was introduced in 2004 ([Bellomo 2007](#)), and to acute kidney injury (AKI) diagnosis and classification criteria, introduced in 2007 ([Mehta 2007](#)). These classifications are generally accepted in modern clinical practice and research ([Lopes 2013](#)). So that the reader might find no uniformity or consistency for the diagnosis or classification of renal damage in many of the older studies included in this review; we have taken the criteria and diagnosis used by the authors. Any future update of this review should include a subgroup of studies conforming to such classification as RIFLE or AKI.

Another area of concern was that we were unable to standardize the administration or withholding of various medications, which may or may not have influenced individual study results.

Agreements and disagreements with other studies or reviews

Results of this review reflect previous versions of the review (Zacharias 2005; Zacharias 2008). A recent systematic review, undertaken to look at renal protection offered by perioperative haemodynamic manipulation, looks at the effects of haemodynamic stabilization and the effects of inotropes and fluids or a combination of these (Brienza 2009). Although we are reluctant to comment on the methodological rigor of the Brienza review, it is of note that this review agrees with the present review on the use of fluids as a measure to protect renal function, showing no clear advantage for fluid management alone. However, the focus of our review is exploration of the effects of pharmacological agents used in the perioperative period.

AUTHORS' CONCLUSIONS

Implications for practice

No convincing evidence suggests that pharmacological or other interventions used to protect the kidneys during surgery are of benefit to patients, as seen from 72 included studies. Reasonable numbers of studies are currently available to substantiate this point. It is also of note that we were unable to find any significant adverse effects associated with the various interventions.

Implications for research

Many studies are available on the use of various pharmaceutical agents to protect renal function during surgery. Further areas of

possible research might include the use of newer methods of identifying acute renal damage, such as urinary biomarkers. Future studies should focus on evaluation of preventive measures or more precise and accurate methods of identifying the benefit or harm of interventions. Use of RIFLE or AKI classification to identify renal damage would result in better comparisons of the effects of interventions and procedures.

Feedback

Please forward any comments and feedback to Jane Cracknell (jane_cracknell@yahoo.com), Managing Editor, Cochrane Anaesthesia Review Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Adabag 2008

Methods	Cardiac surgery patients, with pre-existing chronic kidney disease were studied (GFR <60ml/min.1.73m ²). Excluded patients in severe renal failure, emergency surgery and intravenous contrast within 4 days.
Participants	Intervention group (N-acetylcysteine group), n= 50, Age: mean=70, SD=9. Control group (matching placebo), n=52, Age: mean=72, SD=9.
Interventions	Oral N-acetyl cysteine. 14 doses, twice daily. Started 1 day before surgery, (3 doses before surgery and 11 doses after surgery). Matching placebo for same duration and time used. The 2 groups were comparable.
Outcomes	30 day mortality, acute kidney injury, acute renal injury needing haemodialysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by the investigational (?) pharmacist. Block randomization (blocks of 10).
Allocation concealment (selection bias)	Low risk	Participants, researchers and clinicians blinded to treatment assignment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, researchers and clinicians (including data collecting nurse) were blinded. Drug packets matched in volume, colour, consistency and transparency and given mixed with fruit juice to mask taste.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Amano 1994

Methods	Consecutive patients for coronary artery bypass graft (CABG); randomization done, but method not clear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Glutathione group n = 10, age, mean = 58.2, SD = 2.5; control group n = 9, age, mean 56.8, SD 2.5

Amano 1994 (Continued)

Interventions	Glutathione 200 mg/kg IV before bypass and same dose repeated during 1st and 2nd postoperative days. Control group had saline in the same manner
Outcomes	Urine output, creatinine clearance, fractional excretion of sodium
Notes	No response to letter for details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Randomly assigned' into two groups. No details of randomization given
Allocation concealment (selection bias)	High risk	D - Not used
Blinding (performance bias and detection bias) All outcomes	High risk	None described; control group had no treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Amano 1995

Methods	Consecutive patients for CABG; randomization method not clear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Diltiazem group n = 13, age, mean = 54.5, SD = 1.8; control group n = 10, age, mean = 54.2, SD = 1.6
Interventions	Diltiazem 0.1 mg/kg bolus, followed by infusion of 2 mcg/kg/min until end of aortic cross clamping, followed by nasogastric administration every 8 hours for 24 hrs; control group received 5% dextrose in the same manner
Outcomes	Urine output, creatinine clearance, free water clearance, fractional excretion of sodium
Notes	No response to letter for details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Patients were randomized into either diltiazem or no treatment groups'; no details of randomization method
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	None described; control group had no treatment

Interventions for protecting renal function in the perioperative period (Review)

Amano 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
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Ascione 1999

Methods	Patients having CABG; randomization by card allocation; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Off pump n = 25, age, mean = 59.4, SD = 10.5; control (on pump), n = 26, age, mean = 63.8, SD = 6.7
Interventions	On pump and off pump used for revascularization of coronary arteries
Outcomes	Creatinine clearance
Notes	Inadequate response to letter from the contact author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Prospectively randomized by card allocation'
Allocation concealment (selection bias)	Unclear risk	'Prospectively randomized by card allocation'; no further details given on allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not discussed in text
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed

Barr 2008

Methods	Cardiac surgery patients, over 18 yrs, elective or urgent surgery in patients with chronic renal impairment (preop CCl of under 40ml/min). Excluded renally crippled patients (on dialysis), pregnant or sensitivity to drug used.
Participants	3 intervention groups: Fenoldopam group – 19, NAC group – 20, NAC+ Fenoldopam group – 21, Placebo group - 19. Ages: mean, SD G1 – 77.2, 1.2; G2 – 73.8, 2.2; G3 – 73.5, 2.0; G4 – 72.4, 2.0 Sex (Male/ Female): G1 – 12 / 7; G2 – 15 / 5; G3 – 12 / 9; G4 – 13 / 6
Interventions	Four groups of participants.

Interventions for protecting renal function in the perioperative period (Review)

Barr 2008 (Continued)

Group 1: Fenoldopam 0.1 mcg/kg/min at induction and continued for 48 hrs

Group 2: N-acetyl cysteine orally 600mg per day 1 day preop and on the morning of surgery and the night of surgery.

Group 3: Fenoldopam and N-acetylcysteine together

Group 4: Placebo: Normal saline instead of fenoldopam, for 48 hrs ('double blinded'). Taste controlled placebo instead of NAC, same time

Outcomes	Mortality, acute renal injury (renal replacement therapy), creatinine clearance (Cockcroft-Gault)
Notes	results reported as mean and SE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization done by pharmacy dept; method of randomization uncertain
Allocation concealment (selection bias)	Unclear risk	No specific mention of allocation concealment except to say 'double-blinded'.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No specific mention of who all were blinded; reports as 'Double-blinded', placebo controlled trial. Not sure if blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reports one withdrawal

Berendes 1997

Methods	Patients having CABG; randomization done, method unclear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Dopamine 0.5 mcg/kg/min, n = 10, age, mean = 60, SD = 7.1; dopamine 1 mcg/kg/min, n = 10, age, mean = 62, SD = 8.2; dopamine 2 mcg/kg/min, n = 10, age, mean = 62, SD = 10.2; placebo, n = 14, age, mean = 62, SD = 6.3
Interventions	Different doses of diltiazem, after induction of anaesthesia and for 24 hours post-operation
Outcomes	Creatinine clearance
Notes	Did not contact authors; old study and no additional information required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Placebo controlled prospective study'; no description of randomization
Allocation concealment (selection bias)	High risk	None described

Berendes 1997 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Bergman 2002

Methods	Patients undergoing cardiac surgery with cardiopulmonary bypass; randomization done using list from hospital pharmacy; allocation concealment method unclear; blinding of patients, researchers and care givers is unknown, but strong possibility; study of moderate methodological quality
Participants	Cardiac surgery. diltiazem group, n = 12, age, mean = 72, range, 69-76; placebo group, n = 12; age, mean = 73, range, 69-74. All participants had high serum creatinine
Interventions	Diltiazem 0.25 mg/kg infusion for 15 min, followed by infusion of 1.7 mcg/kg/min for 24 hours
Outcomes	Glomerular filtration rate (GFR)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were consented and randomized; method of randomization not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for drop outs

Burns 2005

Methods	High risk patients undergoing cardiac surgery; randomization by pharmacy by permuted block strategy (alternate blocks of 4 or 6); Allocation concealed by central randomization and drug (or placebo) dispensed by pharmacy by colour and consistency matching; everyone blinded to the nature of drugs
Participants	Cardiac surgery. N-acetyl cysteine, 4 doses or 600mg or placebo 4 doses of 5% dextrose. Intervention group, n = 148, age, mean = 68.9, SD = 8.9; placebo group, n = 147; age = 69.2, SD = 9.7. Three patients from NAC group and 4 patients from placebo group withdrawn
Interventions	N-acetyl cysteine or placebo given. 1st dose after induction of anaesthesia, 2nd dose at end of bypass, 3rd dose at 12 hrs in ICU and 4th dose at 24hrs

Interventions for protecting renal function in the perioperative period (Review)

Burns 2005 (Continued)

Outcomes	Data available only on mortality and acute renal injury
Notes	Contacted the authors successfully for data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization done by pharmacy trial co-ordinator using a permitted block strategy
Allocation concealment (selection bias)	Low risk	Allocation concealment was using central randomization with drugs prepared by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Quadruple blinded (patients, clinicians, data collectors and data analyst)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Account for drop outs in the trial

Carcoana 2003

Methods	Patients for cardiac surgery; randomization by computer generated random number tables by Pharmacy; allocation concealment clearly stated. Patients, researchers and care givers were blinded; study with good methodological quality
Participants	Cardiac surgery. Mannitol group, n = 26, age, mean = 64.3, SD = 8.9; Dopamine group, n = 25, age, mean = 63.8, SD = 9.8; mannitol + dopamine group, n = 25, age, mean = 63.4, SD = 7.8 (this group excluded in review); Placebo group, n = 24, age, mean = 63.3, SD = 8.8;
Interventions	Mannitol 1 g/kg into pump, dopamine 2 mcg/kg/min during surgery or both together as treatment; saline as placebo
Outcomes	Urine output, creatinine clearance
Notes	No further information sought from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Prospective randomized double-blinded and placebo controlled study'. Computer generated random number tables were used
Allocation concealment (selection bias)	Unclear risk	Does not specifically describe it, but quite likely it was concealed allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded manner; drug or saline supplied by the dept investigational pharmacy in a blinded manner; additive for the CPB circuit prime (mannitol or saline, supplied similarly)
Incomplete outcome data (attrition bias)	Low risk	All allocated patients completed the trial (withdrawals before allocation)

Carcoana 2003 (Continued)

All outcomes

Chen 2007

Methods	Adults over 18yrs having cardiac surgery under cardiopulmonary bypass and having pre-existing renal insufficiency (CCl <60ml/min) were studied. Excluded shocked patients and patients with aortic dissection.
Participants	Intervention group: n=17; Age: mean=77, SD=10; Sex: M=12, F=5. Control group: n=19; Age: mean=78, SD=7; Sex: M=10, F=9.
Interventions	Nesiritide infusion 0.005 mcg/kg/min, from start of induction of anaesthesia for 24 hrs. Control group received 'placebo', but not sure what it was. The 2 groups were not comparable.
Outcomes	Mortality, acute renal injury (needing dialysis), and creatinine clearance (Cochroft-Gault formula)
Notes	Data available on plasma cystatin. plasma aldosterone, plasma cGMP and plasma BNP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomized'; no details provided; described as 'double-blind, placebo-controlled proof of concept trial'
Allocation concealment (selection bias)	Unclear risk	No details provided apart from 'double-blind, placebo-controlled proof of concept trial'
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided apart from 'double-blind, placebo-controlled proof of concept trial'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reports 4 withdrawals from trial

Cho 2009

Methods	Patients undergoing robot-assisted laparoscopic radical prostatectomy (RALRP). Excluded patients with chronic renal insufficiency preop
Participants	Intervention group: n=50; Age: mean=67, SD=6. Control group: n=50; Age: mean=68, SD=4
Interventions	Intervention group: Nicardipine infusion - after induction of anaesthesia infusion 0.5mcg/kg/min until end of surgery. Control group: Normal saline infusion at same rate. Both groups were comparable.
Outcomes	Mortality (mention only), calculated GFR, urine output
Notes	Also reports 'renal insufficiency', based on eGFR values only.

Risk of bias

Interventions for protecting renal function in the perioperative period (Review)

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Cho 2009 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization method used
Allocation concealment (selection bias)	Unclear risk	Computer allocation, no further details given (likely to be adequate)
Blinding (performance bias and detection bias) All outcomes	High risk	Not described except the statement 'investigator blinded to the study group evaluated the postoperative data'; likely to be inadequate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Cogliati 2007

Methods	Elective cardiac surgery patients with high creatinine levels ($> 1.5\text{mg/dl}$) (patients with chronic renal failure), more than 70yrs, diabetes on insulin or previous cardiac surgery (at least one of these factors present = high risk pt). Excluded patients who were renal cripples (those on dialysis) and allergy to drug used	
Participants	Intervention group: n=95; Age: mean=70.3, SD=7.6; Sex: M=61; F=34 Control group: n=98; Age: mean=69.6, SD=10.4; Sex: M=63; F=35	
Interventions	Fenoldopam 0.1mcg/kg/min infusion immediately before incision and continued for 24 hrs. Control group: normal saline at the same rate for 24 hrs. Groups were comparable.	
Outcomes	Creatinine clearance (Cochroft-Gault formula), urine output	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization from a computer list, in an envelope
Allocation concealment (selection bias)	Low risk	Sealed envelope used; 'All personnel and patients were blinded to the assignment'
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded nurse, not involved with study, prepared the drug/placebo in identical 50ml filled syringes, 'All personnel and patients were blinded to the assignment'
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant lost to follow-up

Colson 1990

Methods	Patients having CABG; randomization & double blinding stated, but method not specified; method of allocation concealment is unclear; blinding of patients, researchers and care givers is unknown, but possible it was adequate; poor methodological study
Participants	Coronary artery bypass surgery. Captopril group n = 8, age, mean = 56, SD = 3; control group n = 8, age, mean = 60, SD = 2
Interventions	Captopril 100 mg orally tid for 2 days preoperatively, last dose being 2 hrs before surgery; placebo tablets for control group
Outcomes	Renal plasma flow
Notes	Old study; no attempt made to contact authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Allocated in a randomized double-blind fashion to two groups'; No details on randomization method
Allocation concealment (selection bias)	Unclear risk	'Allocated in a randomized double-blind fashion to 2 groups'; no description of method of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details on blinding except 'double-blind fashion'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given in text

Colson 1992

Methods	Patients having abdominal aortic aneurysm (AAA) surgery; randomization and double blinding of treatments done, but method not specified; method of allocation concealment is unclear; blinding of patients, researchers and care givers is unknown, but possible it was adequate; poor methodological quality study
Participants	Abdominal aortic surgery. Enalapril group n = 8, age, mean = 58, SD = 4; nicardipine group n = 8; age, mean = 63, SD = 3; control group n = 8, age, mean = 63, SD = 1
Interventions	Enalapril 10 mg orally BD for 2 days preoperation; placebo capsules for control group
Outcomes	GFR, renal plasma flow; fractional excretion of sodium
Notes	Old study; no attempt made to contact authors. The same study (with alternative treatment is quoted "Colson 1992A")

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Allocated in a randomized double-blind fashion to 2 groups'; No details on randomization method

Colson 1992 (Continued)

Allocation concealment (selection bias)	Unclear risk	'Allocated in a randomized double-blind fashion to 2 groups'; No description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details on blinding except 'double blind fashion'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given in text

Costa 1990

Methods	Patients with pre-operative renal dysfunction (Creatinine clearance less than 50ml/min) having CABG; randomization method not specified; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Coronary artery bypass surgery. Dopamine group n = 12, age, mean = 60.3, SD = 12.3; control group n = 12, age, mean = 61.3, SD = 8.9; dopamine and SNP group, n = 12, age, mean = 54.2, SD = 8.7 (this group excluded from review)	
Interventions	Dopamine infusion 2.5 mcg/kg/min during the operation (unsure for how long); control group had no treatment	
Outcomes	Creatinine clearance, free water clearance, fractional excretion of sodium	
Notes	Old study; no attempt made to contact authors. Excluded parallel treatment group	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly divided into three groups'; no description of randomization
Allocation concealment (selection bias)	High risk	No description of allocation method
Blinding (performance bias and detection bias) All outcomes	High risk	No description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details in text

Cregg 1999

Methods	Idiopathic scoliosis surgery patients; randomization method not specified; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Corrective spinal surgery for scoliosis. Dopamine group, n = 15, age, mean = 14.6, SD = 3.6; control group, n = 15, age, mean = 12.1, SD = 2.8	

Cregg 1999 (Continued)

Interventions	Dopamine infusion 3 mcg/kg/min after induction for 24 hrs; control group received 5% dextrose for 24 hrs
Outcomes	Urine output, fractional excretion of sodium
Notes	Unable to contact the author; the only study selected which is on a paediatric population

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated' into three groups; no description of randomization method
Allocation concealment (selection bias)	High risk	No description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No details on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given

Dawidson 1991

Methods	Consecutive patients for abdominal aortic surgery; randomization by random card method; allocation concealment not used; blinding of patients, researchers and care givers is unknown, but possible; poor methodological quality study
Participants	Corrective abdominal aortic surgery. Dextran 60 group, n = 10, age, mean = 62, SD = 10.4; Ringer's lactate group, n = 10, age, mean = 66.1, SD = 13.7
Interventions	Dextran 60 infusion during operation and Ringer's lactate solution during surgery, ratio being 1:3 for the solutions
Outcomes	Urine output; mortality data
Notes	Too old study to get any more information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomized to either treatment group' by pulling a card from a previously prepared deck
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No details on blinding

Dawidson 1991 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given in text
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de Lasson 1995

Methods	Consecutive patients for abdominal aortic surgery; randomization method unclear; allocation concealment not used; blinding of patients and care givers is unknown, researcher blinded; poor methodological quality study
Participants	Abdominal aortic surgery. Dopamine group n = 12, age, mean = 63; placebo n = 12, age, mean = 60
Interventions	Dopamine infusion 3 mcg/kg/min during operation and for 24 hrs
Outcomes	Urine output, GFR, renal plasma flow, free water clearance
Notes	No reply from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated into infusion of dopamine or placebo' by one of the authors who was unaware of the treatment allocation; method of randomization is not clear in text
Allocation concealment (selection bias)	Low risk	Not sure of any allocation concealment, but likely
Blinding (performance bias and detection bias) All outcomes	High risk	Not described any blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given in text

de Lasson 1997

Methods	Patients for abdominal aortic surgery
Participants	Abdominal aortic surgery. Felodipine group n = 11, age, mean = 65; control group n = 12, age, mean = 60
Interventions	Felodipine 5 mg slow release tab for 5 days preoperatively, last dose 1-2 hrs before surgery; placebo tablets as control
Outcomes	Urine output, GFR, renal plasma flow, free water clearance, fractional excretion of sodium
Notes	No reply from authors

Risk of bias

de Lasson 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization and drug or placebo preparation done by drug company; method not described was central and likely to be good
Allocation concealment (selection bias)	Unclear risk	Not sure of any allocation concealment, but likely possibility
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Possible, but does not describe blinded tables
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient had additional drugs, but not excluded

Dehne 2001

Methods	CABG patients, randomized into four groups. Method of randomization unclear; allocation concealment or blinding not mentioned. Methodological quality poor	
Participants	Aortocoronary bypass surgery. Patients into four groups; Group (1), controls with normal renal function: n = 12; age: mean = 62.6, SD = 8.0; group (2), dopexamine infusion in patients with normal renal function: n = 12; age: mean = 64.0, SD = 7.5; group (3), controls with abnormal renal function: n = 12; age, mean = 62.4, SD = 7.5; group (4), dopexamine infusion in patients with abnormal renal function: n = 12; age, mean = 65.4, SD = 8.1	
Interventions	Dopexamine 1 mcg/kg/min after induction of anaesthesia, until the end of surgery in groups 2 and 4; not sure how the controls were treated	
Outcomes	Urine output, creatinine clearance	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated into two groups, but does not describe the randomization method
Allocation concealment (selection bias)	High risk	Does not describe the allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Does not mention blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in calculations

Donmez 1998

Methods	CABG patients. Patients were randomized, but method of randomization and allocation concealment not described
Participants	CABG patients. All patients received dopamine 2mg/kg/min infusion. Group (1) verapamil 5mg added to prime solution: n = 25; age, mean = 58.3, SE = 1.9; group (2), nimodipine 1-15mcg/kg/min during bypass; n = 25; age, mean = 56.1, SE = 2.6; group (3), control group; normal saline infusion only; n = 25; age, mean = 56.5, SE = 2.0
Interventions	Verapamil 5 mg in prime in group (1); group (2) received infusion of nimodipine 1-15 mcg/kg/min during bypass; group (3), control group received normal saline only
Outcomes	Creatinine clearance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated into three groups'; method of randomization not described
Allocation concealment (selection bias)	Unclear risk	'Randomly allocated into three groups'; method of allocation not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Randomly allocated into three groups'; method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts described in text

Dural 2000

Methods	CABG patients; randomized by opaque sealed envelopes; allocation concealment unclear; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery surgery. Dopamine group n = 12, age, mean = 53.2, SD = 10.9; mannitol group, n = 12, age, mean = 55.4, SD = 8.4; control group, n = 12, age, mean = 53.7, SD = 8.3
Interventions	Dopamine 3 mcg/kg/min started after induction, until end of operation; mannitol 1 mg/kg/hr from induction unto end of operation; no treatment for control group
Outcomes	Urine output
Notes	No reply so far from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated into three groups'; method of randomization not described

Dural 2000 (Continued)

Allocation concealment (selection bias)	Unclear risk	'Randomly allocated into 3 groups'; method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Randomly allocated into 3 groups'; method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Does not describe any dropouts

Durmaz 2003

Methods	Patients for CABG, with renal dysfunction (preoperative creatinine more than 2.5mg/dl)	
Participants	CABG in patients with renal dysfunction. Preoperative dialysis group, n = 21; age, mean = 58.1, SD = 11.8; control group (no preoperative dialysis), n = 23; age, mean = 54.3, SD = 11.1	
Interventions	Preoperative haemodialysis in the intervention group; control group had no preoperative haemodialysis.	
Outcomes	Mortality, acute renal injury	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization done by the last digit of the medical record number of patient (Quasi-randomization)
Allocation concealment (selection bias)	High risk	'Patients were prospectively allocated into 2 groups'
Blinding (performance bias and detection bias) All outcomes	High risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not given in text

Fischer 2005

Methods	CABG. Used retrospective review of data from a randomized, double blinded, trial. No details are given about the method of randomization or allocation concealment, but confirms double-blind status. Methodology poor	
Participants	CABG patients, age: mean = 66, SD = 9. Intervention group received N-acetyl cysteine during bypass, n = 20; placebo group, n = 20, not sure what they received	

Fischer 2005 (Continued)

Interventions	N-acetyl cysteine, 100 mg/kg in prime, followed by 20 mg/kg per hour until end of bypass. Unsure what placebo group received
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Outcomes	Mortality
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Retrospective chart review of a randomized trial in 2003, which used computer generated allocation list (randomly permuted blocks of random size) provided by dept of Medical Statistics
Allocation concealment (selection bias)	Unclear risk	Computer generated allocation list (randomly permuted blocks of random size) provided by dept of Medical Statistics
Blinding (performance bias and detection bias) All outcomes	Low risk	Drugs were supplied in identical looking glass vials containing drug or placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions described in text

Gubern 1988

Methods	Patients for biliary surgery (on patients with some renal impairment); randomization method not detailed; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
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Participants	Biliary tract surgery. Mannitol group n = 17, age, mean = 65.9, SD = 12; control group n = 14, age, mean = 68.5, SD = 9.9
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Interventions	Mannitol 50 g intravenously 1 hour preoperation and for 2 days; Control treatment had no treatment
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Outcomes	Urine output, GFR
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Notes	Study too old to try to obtain details
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Prospectively randomized'; no details of method of randomization
Allocation concealment (selection bias)	Unclear risk	'Prospectively randomized'; no details of method of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Prospectively randomized'; no details of method of blinding

Interventions for protecting renal function in the perioperative period (Review)

Gubern 1988 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Fate of participants discussed
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Haase 2007

Methods	Elective cardiac surgery patients with high creatinine (>150 mcmmol/l), older patients, diabetes on insulin or previous cardiac surgery (at least one of these factors present = high risk patient, but none on dialysis)
Participants	Intervention group: n=30; Age: mean= 68.9, SD=9.7; Sex: M=23, F=7 Control group: n=30; Age: mean=68.3; SD=9.3; Sex: M=21, F=9
Interventions	Intervention group: N-Acetyl cysteine infusion immediately after induction at dose of 150mg/kg over 15 min, followed by continuous infusion of 50mg/kg over 4 hours, then 100mg/kg over 20hrs. Control group: Normal saline at the same rate for 24 hrs
Outcomes	Mortality, urine output, acute renal injury (needing postop renal replacement therapy)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using Microsoft Excel-based random number generation to create a randomization list, in blocks of 10
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured by quadruple-blinding (patients, clinicians, data collectors and data analysers) were unaware of groups or treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	Quadruple-blinding (patients, clinicians, data collectors and data analysers were blinded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	None missed

Haase 2009

Methods	Elective cardiac surgery patients (CPB), with pre-existing renal dysfunction (creatinine >120mmol/L), high risk patients (no patients on dialysis)
Participants	Intervention group: n=50; Age: mean=71.5, SD=9.2; Sex: M=30; F=20 Control group: n=50; Age: mean=70.6; SD=9.5; Sex: M=33, F=17
Interventions	Intervention group: Sodium bicarbonate 0.5mmol/kg in 250ml 5% dextrose bolus immediately after induction of anaesthesia, followed by continuous infusion of 0.15mmol/kg in 1000ml of 5% dextrose over 23 hrs: (Total of 4mmol/kg in 24 hrs)

Haase 2009 (Continued)

Control group: Sodium chloride infusion in a similar fashion for same period (same volume infused)

Outcomes	Mortality (hospital) and requirement for renal replacement therapy
Notes	No missing data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Microsoft Excel based random number generation, with blocks of 10; central randomization by dept of Pharmacy
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved by central randomization, blinding to all researchers, patients and others. Allocation revealed only after data analysis.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both infusions were in separate shrink-wrapped black plastic bags that were identical in appearance (blinded to patients, anaesthetists, surgeons ICU personnel and nurses and others)
Incomplete outcome data (attrition bias) All outcomes	Low risk	One in each group

Halpenny 2002

Methods	Patients for AAA; randomization and blinding mentioned in text, but not detailed; allocation concealment not used; blinding of patients, researchers and care givers is unknown, but possible; overall poor methodological quality study
Participants	Abdominal aortic surgery. Fenoldopam group n = 14, age, mean = 70, SD = 5; control group n = 13, age, mean = 69, SD = 6
Interventions	Fenoldopam infusion 0.1 mcg/kg/min (only during aortic cross clamping); placebo for control group
Outcomes	Urine output, creatinine clearance, free water clearance, fractional excretion of sodium
Notes	No response from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Random allocation used'; method of randomization not given
Allocation concealment (selection bias)	Unclear risk	'Random allocation used'; method of allocation not given
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not described
Incomplete outcome data (attrition bias)	Low risk	Exclusion described

Halpenny 2002 (Continued)

All outcomes

Harten 2008

Methods	Emergency abdominal surgery, age >50yrs. Excluded night cases, patients on lithium and those having vascular surgery
Participants	Intervention: n=14; Age: median=66, range=56-75; Sex: M=11, F=3 Control: n=15; Age: median=64, range=51-76; Sex: M=12, F=3
Interventions	Intervention: Optimization of intraoperative fluids using arterial line and Lidco cardiovascular monitoring and gave fluid boluses of 250ml 6% hydroxyethyl starch over 15 min done as necessary Control: Standard care, fluids decided by clinicians in Operating Theatre. Groups not comparable
Outcomes	Mortality (30 days) and renal morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized', but no details given
Allocation concealment (selection bias)	Unclear risk	Allocated to control and intervention group using opaque envelopes immediately before surgery; not sure if allocation concealment was adequate
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 died before operation in the intervention group

Hynninen 2006

Methods	Elective repair of AAA. Excluded patients with renal insufficiency (creatinine >130mmol/l) and those who had renal artery clamping done during surgery
Participants	Intervention group: n=34; Age: mean=66, SD=10; Sex: M=27; F=7 Control group: n=35; Age: mean=67, SD=10; Sex: M=27, F=8
Interventions	Intervention: N-Acetyl cysteine infusion, 150mg/kg NAC in 250ml 5% dextrose in 20min (bolus) after induction of anaesthesia, followed by 150mg/kg in 250ml 5% dextrose, infused over 24 hrs. Control: 250ml 5% dextrose in 20min, followed by 250ml 5% dextrose infusion for 24hrs

Hynninen 2006 (Continued)

Outcomes Mortality, patients needing renal replacement therapy (dialysis), urine output, urinary NAG/creatinine ratio, urinary albumin/ creatinine ratio, plasma Cystatin C

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized in blocks of 10, done by hospital pharmacy, no details given
Allocation concealment (selection bias)	Low risk	Allocation was done by hospital pharmacy. None of the clinical and study personnel was aware of study allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Likely that there was blinding, though not detailed in text
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One patient withdrew from study intraoperatively, does not mention which group, though most likely the intervention group (as seen from the numbers in each group)

Kaya 2007

Methods Cardiac surgery patients, with eGFR >30ml/min, LVEF <0.50 and a minimum of 2 lesions undergoing CABG. Excluded patients with CCF, cardiogenic shock, unstable angina, MI and renal cripples (on dialysis or creatinine >300mmol/l)

Morbidly obese

Participants Intervention group: n=124; Age: mean=60.8, SD=10.8. Sex: M=81, F=43

Control group: n=116; Age: mean=61.3, SD=9.7; Sex: M=72, F=44

Interventions Intervention: Sodium nitroprusside (SNP) infusion. SNP started with onset of rewarming 0.1mcg/kg/hr, until end of CPB. SNP in 50ml blinded syringe

Control: Normal saline in 50ml blinded syringe

Outcomes Mortality, renal injury, eGFR

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization done by statistician
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed, envelopes
Blinding (performance bias and detection bias)	Low risk	SNP and saline in uniformly appearing 50ml syringes, blinded to surgeons, perfusionists and nurses; the investigators did not know the details

Interventions for protecting renal function in the perioperative period (Review)

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Kaya 2007 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported as none
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Kleinschmidt 1997

Methods	CABG patients. Three groups, randomization not described, no indication of concealment allocation, but indicated double-blind status. Methodological quality poor
Participants	CABG. Pentoxifylline group, n = 14, age, mean = 61.7, SD = 8.0; gamma-hydroxybutyrate group, n = 13, age, mean = 62.3, SD = 3.9; control group, n = 13, age, mean = 62.9, SD = 6.2
Interventions	Pentoxifylline 1 mg/kg bolus, followed by 1 mg/kg/hour during operation. Gamma hydroxybutyrate bolus of 25 mg/kg, followed by 25 mg/kg/hour during operation. Control group received normal saline infusion
Outcomes	Creatinine clearance, fractional excretion of sodium
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by computer
Allocation concealment (selection bias)	High risk	Not described in detail
Blinding (performance bias and detection bias) All outcomes	High risk	Not described in detail
Incomplete outcome data (attrition bias) All outcomes	High risk	Not described

Kramer 2002

Methods	Patients for CABG; randomized and double-blinded study; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Theophylline group n = 28, age, mean = 60.4, SD = 10.1; control group n = 28, age, mean = 60.3, SD = 8.1
Interventions	Theophylline bolus of 4 mg/kg over 30 min, followed by infusion of 0.25 mg/kg/hr for 96 hrs; control group received saline
Outcomes	GFR

Kramer 2002 (Continued)

Notes No response from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized to receive one of two treatments
Allocation concealment (selection bias)	High risk	No details given
Blinding (performance bias and detection bias) All outcomes	High risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Early termination of study in 33 of 56 patients; Intention to treat (ITT) analysis used

Kulka 1996

Methods	Patients for CABG; randomization method not described; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Coronary artery bypass surgery. Clonidine group n = 23, age, mean = 58, SD = 7; control n = 25, age, mean = 57, SD = 2
Interventions	Preoperative infusion of clonidine 4 mcg/kg over 15 min, 1 hr before surgery; placebo in control group
Outcomes	Urine volume, creatinine clearance
Notes	No response from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Allocated into two groups in a double-blinded randomized fashion'; no details of randomization given
Allocation concealment (selection bias)	Unclear risk	'Allocated into 2 groups in a double-blinded randomized fashion'; no details of allocation given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Allocated into 2 groups in a double-blinded randomized fashion'; no details of blinding given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients were excluded

Lassnigg 2000

Methods	Patients undergoing cardiac surgery; randomization by sealed envelopes; allocation concealment unclear, but strong possibility; blinding of patients, researchers and care givers done; good methodological quality study
Participants	Cardiac surgery. Dopamine group n = 42, age, mean = 63, SD = 10; frusemide (furosemide) group n = 41, age, mean = 63, SD = 10; control group n = 40, age, mean = 65, SD = 10
Interventions	Dopamine infusion 2 mcg/kg/min for 48 hrs; 05 mcg/kg/min frusemide infusion for 48 hrs; saline in control group
Outcomes	Urine volume, creatinine clearance, fractional excretion of sodium
Notes	Same study (with alternative treatment) is quoted in "Lassnigg 2000A"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Placebo controlled randomized double blind trial; block randomization done and used sealed envelopes; no further details of randomization
Allocation concealment (selection bias)	Low risk	Placebo controlled randomized double blind trial; block randomization done and used sealed envelopes; no further details of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo controlled randomized double blind trial; block randomization done and used sealed envelopes; no details of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients were excluded from analysis

Lau 2001

Methods	Abdominal aortic repair patients. Randomization done, but method not specified. Allocation concealment unclear or not done. Poor methodological quality
Participants	AAA repair. Intervention is extraperitoneal approach; n = 10; age, mean = 69.8, SEM=3.1. Control group is intraperitoneal approach; n=10; age, mean=74.3, SEM=2.5
Interventions	Extraperitoneal approach for AAA repair compared with transperitoneal approach
Outcomes	Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Recruited patients were allocated to one of two groups'; no details on randomization
Allocation concealment (selection bias)	Unclear risk	'Recruited patients were allocated to one of 2 groups'; no details on allocation

Lau 2001 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	'Recruited patients were allocated to one of 2 groups'; no details of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients accounted for

Licker 1996

Methods	Infrarenal aortic surgery; randomization method not clear; allocation concealment not used; blinding of patients, researchers and care givers is unknown, but likely; overall poor methodological quality study	
Participants	Abdominal aortic surgery. Enalapril group n = 11, age, mean = 69; control group n = 9, age, mean = 68	
Interventions	Enalapril bolus 50 mcg/kg injection 25 min before anaesthesia; saline injection in control group	
Outcomes	Urine output, creatinine clearance, renal plasma flow, free water clearance, fractional excretion of sodium	
Notes	Contacted authors to confirm or exclude duplicate reporting; no response; used only full publication in review	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were allocated in a randomized double-blind manner'; no details of randomization given
Allocation concealment (selection bias)	Unclear risk	'Patients were allocated in a randomized double-blind manner'; no details of allocation given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Patients were allocated in a randomized double-blind manner'; no details of blinding given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients were excluded from trial

Loef 2004

Methods	CABG surgery. Method of randomization unclear, allocation concealment not stated, double-blind status stated. Methodological quality moderately poor	
Participants	CABG surgery. Dexamethasone group, n = 10, age, mean = 67.7, range = 58-76; control group, n = 10, age, mean = 59.6, range = 47-76	
Interventions	Dexamethasone 1 mg/kg before induction of anaesthesia, followed by 0.5 mg/kg 8 hours later. Control group received a placebo, nature of which is unsure	

Loef 2004 (Continued)

Outcomes	Urine output, creatinine clearance, free water clearance, fractional excretion of sodium
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomized in a double blind fashion'; no details of randomization given
Allocation concealment (selection bias)	High risk	'Randomized in a double blind fashion'; no details of allocation given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Randomized in a double blind fashion'; no details of blinding given
Incomplete outcome data (attrition bias) All outcomes	Low risk	'All patients completed the trial'

Marathias 2006

Methods	Cardiac surgery (open heart) in patients with high creatinine. Randomization done, but method unclear. Allocation concealment not stated. Poor methodological quality
Participants	Open heart surgery in patients with renal impairment (high creatinine). Intervention was fluid hydration preoperatively for 12 hours using half normal saline; n = 30; age, mean = 64, SEM = 1.7. Control group had fluid restriction for 12 hours preoperatively; n = 15; age, mean = 64.2, SEM = 2.8
Interventions	Preoperative fluid hydration using half isotonic saline, 1 ml/kg/hour for 12 hours; control group had no fluid hydration
Outcomes	Mortality, acute renal injury
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Used a 2:1 ratio of randomization process, patients were randomized into groups; no other details of randomization given
Allocation concealment (selection bias)	High risk	Patients were randomized into groups; no other details of allocation given
Blinding (performance bias and detection bias) All outcomes	High risk	Used a 2:1 ratio of randomization process, patients were randomized into groups; no details of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Not described

Interventions for protecting renal function in the perioperative period (Review)

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Mitaka 2008

Methods	Repair of AAA (elective) in patients over 20yrs. Excluded patients on chronic dialysis and those with a preop creatinine >3.0mg/dl
Participants	Intervention group: n=20; Age: mean=69.4, SD=7.7; Sex: M=18, F=2 Control group: n=20; Age: mean=73.3, SD=8.6; Sex: M=17, F=3
Interventions	Intervention: hANP (Atrial natriuretic peptide) infusion, 0.01mcg/kg/min starting dose (to prevent hypotension), increasing by 0.01mcg/kg/min every 10min until dose of 0.05mcg/kg/min is reached. Start infusion of hANP just before cross clamping and continued for 48hrs Control group: Placebo infusion started at 2ml/hr, increased by 2ml every 10min, until 10ml/hr
Outcomes	Acute renal injury (needing dialysis), creatinine clearance, urinary NAG, urine volume
Notes	No data in paper for creatinine clearance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized into two groups'; not sure what method of randomization was used
Allocation concealment (selection bias)	Unclear risk	Not sure how the allocation was done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Blind infusion was performed'; not sure about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described in paper

Morariu 2005

Methods	CABG patients. Intervention dexamethasone IV; randomized, but method of randomization unclear. Allocation concealment not stated, but patients were double-blinded. Methodological quality poor
Participants	CABG patients. Intervention was dexamethasone and control group received a placebo, the nature of which is unclear. Dexamethasone group; n = 10; age, mean = 67.8, 95% CI = 63.4-72.1. Control group, n = 10; age, mean = 59.5; 95% CI = 53.4-65.5
Interventions	Dexamethasone 1 mg/kg at induction, followed by 0.5 mg/kg 8 hours later; placebo in the control group at the same time
Outcomes	Mortality
Notes	

Risk of bias

Morariu 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Designed as a prospective double-blind placebo controlled randomized trial'; no other details of randomization provided
Allocation concealment (selection bias)	High risk	'Designed as a prospective double-blind placebo controlled randomized trial'; no description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Designed as a prospective double-blind placebo controlled randomized trial'; but no other details of blinding provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	'All patients completed the trial'

Morgera 2002

Methods	High risk patients for CABG; randomization not described; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Coronary artery bypass surgery. Prostaglandin group n = 17, age, mean = 62, SD = 5.5; control group n = 17, age, mean = 61, SD = 7	
Interventions	Prostaglandin infusion 2 ng/kg/min at start of anaesthesia and for 48 hrs; control group treatment not described	
Outcomes	Urine volume, creatinine clearance	
Notes	No response to letter	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no other details given
Allocation concealment (selection bias)	High risk	'Patients were randomized'; no mention of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	'Patients were randomized'; no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two people were excluded from analysis

Myles 1993

Methods	Patients for CABG; randomization by random number generated by pharmacy; allocation concealment adequate; blinding of patients, researchers and care givers are adequate; good methodological quality study
Participants	Coronary artery bypass surgery. dopamine group n = 25, age, mean = 62.2, SD = 8; control group n = 24, age, mean = 61, SD = 10
Interventions	Dopamine infusion 3 mcg/kg/min for 24 hrs; 5% dextrose infusion for control group
Outcomes	Urine output, creatinine clearance
Notes	No need for further information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by use of a table of random numbers; 'prospective double-blind randomized trial'
Allocation concealment (selection bias)	Low risk	Coded 50ml syringes from the pharmacy, with contents remaining unknown to investigators until the end of trial; allocation concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Coded 50ml syringes from the pharmacy, with contents remaining unknown to investigators until the end of trial; blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 withdrawals before start of trial

Nicholson 1996

Methods	Consecutive patients for AAA surgery; randomization by sealed envelope (random number); allocation concealment adequate; blinding of patients done, but that of researchers and care givers unknown, but is possible; moderate methodological quality study
Participants	Abdominal aortic surgery. Mannitol group n = 15, age, mean = 68; control group n = 13, age, mean = 71
Interventions	Mannitol 0.3 g/kg before cross-clamp; normal saline for control group
Outcomes	Urine output, creatinine clearance
Notes	Need for further information uncertain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Prospective randomized trial'; no further details on randomization
Allocation concealment (selection bias)	High risk	'Prospective randomized trial'; no details on allocation

Nicholson 1996 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	'Prospective randomized trial'; no details on blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	None reported

Nouri-Majalan 2009

Methods	Elective CABG surgery patients with renal impairment (GFR < 60ml/min), age >18yrs. Excluded emergency CABG surgery patients	
Participants	Intervention group: n=30; Age: mean=65, SD=9.5; Sex: M=17, F=13 Control group: n=30; Age: mean=61, SD=7.9; Sex: M=14, F=16	
Interventions	Intervention: Vitamin E 100 units QID and allopurinol 100mg BD, for 3-5 days preop Control group: Had no treatment	
Outcomes	Mortality, ARF (needing dialysis)	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no further details
Allocation concealment (selection bias)	Unclear risk	No indication of allocation concealment, but for statement 'to prevent bias surgeons, nurses, and lab technicians were blinded to patient assignment'
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Possible: states, 'to prevent bias surgeons, nurses, and lab technicians were blinded to patient assignment'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None indicated in text

O'Hara 2002

Methods	Partial nephrectomy in patients with single kidney; Randomization mentioned in text, no details given; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Partial nephrectomy. Dopamine group n = 13, age, mean = 64.6, SD = 8; Control group n = 11, age, mean = 62.4, SD = 8.8	

O'Hara 2002 (Continued)

Interventions	Dopamine infusion 3 mcg/kg/min during surgery and for 1 hr afterwards; no intervention in control group
Outcomes	Urine output, GFR, renal blood flow
Notes	No response to letter

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Prospective randomized study'; no further details on randomization
Allocation concealment (selection bias)	High risk	'Prospective randomized study'; no details on allocation
Blinding (performance bias and detection bias) All outcomes	High risk	'Prospective randomized study'; no details on blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 out of 35 excluded

Parks 1994

Methods	Surgery for obstructive jaundice; randomized, but no details given. allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Elective surgery for obstructive jaundice. Control group, n = 10, age not given; dopamine group, n = 13, age not given
Interventions	Control group had pre-op IV fluids and frusemide on induction; dopamine group had the above + infusion of dopamine 3 mcg/kg/min for 48 hours
Outcomes	Urine output, creatinine clearance
Notes	Old study, no real need for further information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomly allocated into two groups'; no further details on randomization
Allocation concealment (selection bias)	High risk	'Patients were randomly allocated into 2 groups'; no details on allocation
Blinding (performance bias and detection bias) All outcomes	High risk	'Patients were randomly allocated into 2 groups'; no details on blinding

Parks 1994 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Not disclosed
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Perez 2002

Methods	Laparoscopic colorectal surgery; randomization done by use of sealed envelopes; allocation concealment not used; blinding of patients, researchers done, but that of care givers is unknown; overall good methodological quality study (unfortunately no relevant observations useful for this review)
Participants	Elective laparoscopic colorectal surgery patients. Dopamine group, n = 19, age, mean = 64.3, SD = 9.4; control group, n = 18, age, mean = 61.3, SD = 16.7
Interventions	Dopamine infusion, 2 mcg/kg/min during the operation; control group received saline in the same manner
Outcomes	Urine output, creatinine clearance
Notes	Mailed authors for data because only the difference is given in the text. the data from authors contains details only during and for 2 hours after the operations. Continuous data not suitable for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization performed by aleatorized numbers prepared in closed envelopes'.
Allocation concealment (selection bias)	Unclear risk	No details on concealment of allocation except 'Randomization performed by aleatorized numbers prepared in closed envelopes'; possible to have concealment of allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Drug or placebo given with an identical container in a double blind manner and the volume of drug or saline were same.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients were excluded

Prasad 2010

Methods	Elective OP-CABG surgery patients, with baseline creatinine >133mcmol/l. Inclusion and exclusion criteria detailed in text.
Participants	Intervention group: n=35; Age: mean=55.6, SD=10.2. Sex: M=25; F=10 Control group: n=35; Age: mean=57.8, SD=9.4; Sex: M=28, F=7
Interventions	Intervention: N-acetylcysteine (NAC). Oral NAC 600mg BD on preop day, followed by IV NAC 600mg prior to induction of anaesthesia and IV NAC 600mg BD for 2 postop days (total dose of NAC = 4.8g) Control: No treatment

Prasad 2010 (Continued)

Outcomes Postop renal dysfunction (judged by rise of more than 44 mmol/l or 25% in creatinine from preop values), GFR (Cockcroft-Gault formula)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, prospective, open label study; random number generated from a random number table
Allocation concealment (selection bias)	High risk	No concealment of assignment discussed
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding discussed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four people excluded after randomization

Prowle 2012

Methods Elective high risk cardiac surgery patients (Patients with high creatinine >1.2mg/dl, older than 70yrs, ICHF, ILV EF<35%, diabetes on insulin or previous cardiac surgery; at least one of these factors present)

Participants Intervention group: n=50; mean age= 69.0; SD=11.1; Sex: M = 33; F=17
Control group: n=50; mean age= 67.3; SD=10.8; Sex: M = 37; F=13

Interventions Intervention group: Atorvastatin 40 mg orally a day before surgery and 3 further doses orally in the post op days 1,2 and 3
Control group: Matching placebo for same duration and time

Outcomes Mortality; Acute kidney injury needing dialysis; Rise in Serum creatinine levels; Urinary NGAL, and urinary NGAL/urinary creatinine ratio; Rise in serum transminases and serum creatine kinase

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by the hospital pharmacy clinical trials coordinator. Microsoft excel –based random number generator-permuted block strategy with blocks of 10
Allocation concealment (selection bias)	Low risk	Allocation stratified into two groups based on preop use of statins. Allocation concealed to patients, anaesthetists, cardiac surgeons, intensive care specialists, bedside nurses and investigators

Prowle 2012 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind". Atorvastatin or placebo medication was prepared in capsules of identical appearance and blinded to patients, anaesthetists, cardiac surgeons, intensive care specialists, bedside nurses and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight in intervention group and seven in control

Pull Ter Gunne 1990

Methods	Patients undergoing AAA surgery; randomized, method not described; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Aortic surgery for aneurysm. Preoperative hydration group, n = 11, age, mean = 65, SD, 9. Control group, n = 8, mean = 71, SD = 10	
Interventions	Treatment group optimally hydrated preoperatively (guided by PCWP); control treatment no special treatment	
Outcomes	Creatinine clearance	
Notes	Unlikely to get authors to respond after this long after the study	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Random assignment into two groups'; no further details of randomization
Allocation concealment (selection bias)	Unclear risk	'Random assignment into 2 groups'; the anaesthesiologist was aware of the allocation and treatment received; no further details on allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	'Random assignment into 2 groups'; the anaesthesiologist was aware of the allocation and treatment received; no further details on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided

Ristikankare 2006

Methods	Cardiac surgery patients with high creatinine levels (abnormal renal function). Randomization and allocation concealment methods not stated, but done by hospital pharmacy. Double-blind status stated. Methodological quality moderately good	
Participants	Cardiac surgery (bypass) patients. N-acetyl cysteine group, n = 38, age, mean = 72, range = 44-87; control group, n = 42, age, mean = 69, range = 51-81	
Interventions	N-acetyl cysteine group received loading dose of the drug 150 mg/kg in 15 min, followed by 50 mg/kg for next 4 hours, thereafter 100 mg/kg for next 16 hours. Placebo group received similar amount of saline (0.9%) over the same time	

Interventions for protecting renal function in the perioperative period (Review)

Ristikankare 2006 (Continued)

Outcomes	Mortality, acute renal injury	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	‘Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications’
Allocation concealment (selection bias)	Unclear risk	‘Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications’; but no further details of allocation concealment provided in text
Blinding (performance bias and detection bias) All outcomes	Unclear risk	‘Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications’; no details of blinding provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients were excluded

Ryckwaert 2001

Methods	Cardiac surgery patients; randomized, but method not specified; allocation concealment unclear; blinding of patients, researchers and care givers is unknown, but is likely; overall poor methodological quality study	
Participants	Cardiac surgery (CABG). Enalapril group n = 7, mean = 60.1, SD = 3.6; control group n = 7, age, mean = 66.3, SD = 4.2	
Interventions	Enalapril, 1 mg, 6 hourly for 2 days	
Outcomes	Urine output, GFR, renal plasma flow	
Notes	Unable to contact authors	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘Patients were allocated in a randomized double-blind fashion to two groups’; no further details of randomization given
Allocation concealment (selection bias)	Unclear risk	‘Randomly allocated to two groups receiving blind infusion of drug or placebo’; No other details on allocation method
Blinding (performance bias and detection bias) All outcomes	Low risk	‘Randomly allocated to two groups receiving blind infusion of drug or placebo’; No other details on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No drop outs detailed in text

Sezai 2000

Methods	CABG patients. Randomization done, but details unclear. Allocation concealment not detailed. Blinding is done. Methodological quality moderately good
Participants	CABG patients. Atrial natriuretic peptide group, n=20, age, mean = 62.1, SD = 7.9; control group, n = 20, age, mean = 64.8, SD = 5.2
Interventions	Intervention group received atrial natriuretic peptide infusion, 0.03-0.05 mcg/kg/min for 20 hours, starting during operation, then reduced to 0.02 mcg/kg/min for another 4 hours. Control group received placebo (nature not described). All patients received dopamine and dobutamine at the end of bypass
Outcomes	Urine output, GFR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; No other details on randomization method
Allocation concealment (selection bias)	Unclear risk	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; No other details on allocation method
Blinding (performance bias and detection bias) All outcomes	Low risk	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; No other details on blinding, but likely to be adequate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described, but probably there were no dropouts

Sezai 2009

Methods	CABG surgery. No patients with renal impairment (determined by Cr <1.3 mg/dl and CCr <80ml/min) were included
Participants	Intervention group: n=251; Age: mean=65.6, SD=0.6; Sex: M=193, F=58 Control group: n=253; Age: mean=66.3, SD=0.6; Sex: M=205, F=48
Interventions	Intervention: hANP (Human atrial natriuretic peptide) infusion of hANP 0.02mcg/kg/min from start of CPB, reduced to 0.01mcg/kg/min after start of oral medications and then stopped after 12hrs Control: Normal saline infusion in the same fashion
Outcomes	ARF needing dialysis, mortality, creatinine clearance, fractional excretion of sodium, free water clearance, urine output
Notes	Too many confounders in the intervention and control groups such as use of dopamine infusion in some patients

Sezai 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated into 2 groups by drawing lots
Allocation concealment (selection bias)	Unclear risk	'Randomly allocated by drawing lots'; no other details
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	No mention of dropouts in the text

Sezai 2011

Methods	Randomly allocated into 2 groups by lottery method
Participants	Intervention group: n=141; age: 68.8, SD: 6.7; Males: 123/141 Control group: n=144; age: 68.8, SD: 7.8; Males 128/144
Interventions	Intervention: Carperitide (hANP) infusion, 0.01mcg/kg/min for over 2 days Control: Saline infusion for similar period
Outcomes	Mortality, Acute renal injury needing dialysis, calculated GFR
Notes	Poor quality study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Lottery method'
Allocation concealment (selection bias)	High risk	No evidence of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	None used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts discussed

Shackford 1983

Methods	Patients for aortic reconstruction; randomized by random number method; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Elective aortic reconstruction surgery. Hypertonic saline group, n = 30, age, mean = 60.5, SD = 8.2; Ringer's lactate group, n = 28, age, mean = 61.7, SD = 8.5
Interventions	Hypertonic saline intraoperatively and Ringer's lactate solution intraoperatively
Outcomes	Urine output, creatinine clearance, fractional excretion of sodium
Notes	Very old study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned by random number to one of 2 groups; no details on randomization
Allocation concealment (selection bias)	High risk	Patients were assigned by random number to one of 2 groups; no details on concealment of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Patients were assigned by random number to one of 2 groups; no details on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts described

Shim 2007

Methods	Cardiac surgery (off-pump coronary artery surgery). Randomization using computer generated randomization table. Allocation concealment not stated, but blinding seems adequate. Methodological quality moderately good
Participants	Off-pump coronary artery surgery. Mannitol group, n = 25, age, mean = 63, SD = 8; control group, n = 25, age, mean = 63, SD = 8
Interventions	Mannitol 0.5 g/kg in 10 min during grafting; control group 2.5 ml/kg normal saline during the same time period
Outcomes	Acute renal injury
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Patients were randomly allocated to one of 2 groups using a computer generated randomization table'

Shim 2007 (Continued)

Allocation concealment (selection bias)	Low risk	Patients were randomly allocated to one of 2 groups using a computer generated randomization table; no further details on allocation concealment; likely to be adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	All medical personnel involved in the study were blinded to the contents of the infusion bottle.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts recorded

Song 2009

Methods	Cardiac surgery patients, mostly off pump CABG.	
Participants	Adults undergoing CABG	
Interventions	EPO 300u/kg given immediately following induction of anaesthesia. Same volume of normal saline given as placebo.	
Outcomes	Acute kidney injury was primary outcome (serum creatinine rise of more than 50%); urine output and creatinine clearance (calculated)	
Notes	EPO study. All enrolled patients completed the study.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization done by research unit of hospital. Randomization was stratified by creatinine levels
Allocation concealment (selection bias)	Low risk	Allocation was via Internet
Blinding (performance bias and detection bias) All outcomes	Low risk	None of the clinicians, patients or researchers were aware of the nature of the drugs; matching syringes of EPO and normal saline used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the trial

Tang 1999

Methods	Consecutive patients for CABG; randomization method unclear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Coronary artery bypass surgery. Dopamine group n = 20, age, mean = 61, SD = 10.3; control group n = 20, age, mean = 56.3, SD = 8.7	
Interventions	Dopamine infusion, 2.5-4 mcg/kg/min for 48 hrs; control group without any intervention	

Interventions for protecting renal function in the perioperative period (Review)

Tang 1999 (Continued)

Outcomes	Urine output
Notes	No need to contact authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospectively randomized; no details given
Allocation concealment (selection bias)	High risk	No details of allocation provided in text
Blinding (performance bias and detection bias) All outcomes	High risk	No details of blinding provided in the text
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts recorded

Tang 2002

Methods	Coronary artery surgery. Randomization done, but method not clear. No evidence of allocation concealment or blinding. Methodological quality poor
Participants	Coronary artery surgery. Beating heart surgery group, n = 20, age, mean = 64.8, SD = 6.9; conventional bypass group (control), n = 20, age, mean = 62.1, SD = 9.3
Interventions	Intervention is off-pump coronary artery surgery and control group is on pump coronary artery surgery
Outcomes	Mortality, acute renal injury
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no further details on randomization
Allocation concealment (selection bias)	High risk	'Patients were randomized'; no further details on allocation
Blinding (performance bias and detection bias) All outcomes	High risk	2 different types of procedures; no blinding possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 people were subsequently excluded from trial

Thompson 1986

Methods	Surgery for obstructive jaundice. Randomized, but method of randomization, allocation concealment and blinding not stated. Methodological quality poor
Participants	Surgery for obstructive jaundice. Oral ursodeoxycholic acid group, n = 20, age, mean = 57.0, range = 18-72. Control group, n = 20, age, mean = 56.5, range = 45-78
Interventions	Intervention oral ursodeoxycholic acid 900 mg, 8 hourly for 48 hours in the immediate preoperative period. Control group had no additional treatment
Outcomes	Mortality, acute renal injury, creatinine clearance
Notes	Too old study to contact authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no more details
Allocation concealment (selection bias)	High risk	'Patients were randomized'; no account of allocation method
Blinding (performance bias and detection bias) All outcomes	High risk	'Patients were randomized'; no details on blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	'There were no withdrawals'

Turner 2008

Methods	Patients for elective AAA (infrarenal) repair. Excluded patients on steroids, diabetic patients and those with CRF (Creatinine >150mcmol/l)
Participants	Intervention group: n=10; Age: mean=69.1, SD=5.4; Sex: not described Control group: n=10; Age: mean=71.9, SD=6.0; Sex: not described
Interventions	Intervention: Methyl prednisolone 10mg/kg in 500ml 5% dextrose, infusion over 30min, but mentions only that infusion was given 'during the surgery'; not sure when Control group: Received 5% dextrose solution
Outcomes	Mortality, NAG/creatinine ratio
Notes	Also did serum creatinine, cytokines, alpha-1 microglobulin/ creatinine ratio and albumin/ creatinine ratio

Risk of bias

Bias	Authors' judgement	Support for judgement
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Turner 2008 (Continued)

Random sequence generation (selection bias)	Low risk	Randomization done using computer generated randomization list
Allocation concealment (selection bias)	Low risk	Computer generated randomization list placed in sealed envelopes and opened in numerical order by a third party preparing the study infusion
Blinding (performance bias and detection bias) All outcomes	Low risk	Third party prepared the infusion. The infusions were such that the volumes were equal in the bag and identical colour and the contents of bag were indistinguishable; the infusion was done over 30min to avoid any haemodynamic effects of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Yes, none lost to follow-up

Urzua 1992

Methods	CABG surgery. Quasi randomization by using last digits of their notes, no allocation concealment or blinding
Participants	CABG. Phenylephrine group, n = 7, age, mean = 55, SD = 7. Control group, n = 14, age, mean = 54, SD = 7
Interventions	Intervention is to maintain mean perfusion pressure above 70 mmHg during surgery. Control group had no intervention
Outcomes	Acute renal injury, urine output, creatinine clearance, free water clearance, fractional excretion of sodium
Notes	To old study to contact authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned into one of 2 groups, according to the last digit of their clinical history number (Quasi-randomization)
Allocation concealment (selection bias)	High risk	Allocation by last digit of clinical history number is impossible to conceal
Blinding (performance bias and detection bias) All outcomes	High risk	No report of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	'All patients completed the trial'

Wahbah 2000

Methods	Patients for biliary surgery; randomization method unclear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
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Wahbah 2000 (Continued)

Participants	Biliary tract surgery. Dopamine group n = 10, age, median = 50, range = 37-60; control group n = 10, age, median = 44.5, range = 36-60; dopamine + mannitol group n = 10, age, median = 51, range = 44-58; dopamine + frusemide (furosemide) group n = 10, age, median = 61, range = 55-71 (excluded the last 2 groups from review)
Interventions	Dopamine infusion 2.5 mcg/kg/min during surgery and for 2 days; control group had no treatment
Outcomes	Urine output, creatinine clearance
Notes	No need to contact authors. Excluded 2 parallel treatment groups in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomly allocated into 4 equal groups'; no further details on randomization
Allocation concealment (selection bias)	Unclear risk	'Patients were randomly allocated into 4 equal groups'; no further details on allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No description of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	None described

Welch 1995

Methods	Infrarenal aortic surgery; Randomization method not described; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study
Participants	Abdominal aortic surgery. Dopexamine group n = 15, age, mean = 63.5; control group n = 17, age, mean = 62.1
Interventions	Dopexamine 2 mcg/kg/min infusion during surgery; saline in control group
Outcomes	Creatinine clearance
Notes	Need to contact authors uncertain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomly assigned'; no further details on randomization method used
Allocation concealment (selection bias)	High risk	'Patients were randomly assigned'; no further details on allocation method used
Blinding (performance bias and detection bias)	High risk	No description of blinding

Welch 1995 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	None described
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Wijnen 2002

Methods	AAA surgery (infrarenal). Randomized, but method of randomization, allocation concealment and blinding not stated in the text. Methodological quality poor
Participants	Elective AAA repair. Antioxidant group, n = 20, age, mean = 67, range = 51-75; control group, n = 22, age, mean = 70, range = 59-82
Interventions	Intervention was multiple antioxidant therapy as follows: vitamin E 200 mg orally for 5 days before surgery + vitamin C 200 mg orally on morning of surgery + allopurinol 300 mg orally 1 day before surgery and 300 mg at induction + N-acetyl cysteine 150 mg/kg bolus, followed by infusion of 200 mg/kg over 12 hours preoperatively + mannitol 10%, 500 ml over 12 hours from the time of surgery. Control group had no intervention
Outcomes	Creatinine clearance

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no further details on method of randomization used
Allocation concealment (selection bias)	High risk	'Patients were randomized'; no details on method of allocation used
Blinding (performance bias and detection bias) All outcomes	High risk	No details on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One death described, but not of any dropouts

Witczak 2008

Methods	Elective CPB surgery patients studied. Males with creatinine >150mcmol/L and females >130mcmol/L CABG or valve surgery were included. Excluded patients with unstable angina, EF <35%, renal cripple (on dialysis) or renal transplant patients.
Participants	Intervention: n=10; Age: mean=67.7, SD=9.0; Sex: M=8, F=2 Control: n=10; Age: mean=65.8, SD=10.6; Sex: M=8, F=2

Witczak 2008 (Continued)

Interventions	Intervention: Infusion of nifedipine, from start of surgery and for 24hrs; Nifedipine infusion rate was 0.25 – 0.60 mcg/kg/min (adjusted according to BP)	
	Control: No treatment	
Outcomes	Creatinine clearance	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were ‘randomized’. It appears that the anaesthesiologist ‘randomly drew an envelope with the assigned treatment’
Allocation concealment (selection bias)	High risk	Allocation concealment was possible only for patients and statistician
Blinding (performance bias and detection bias) All outcomes	High risk	No; control had no treatment; only the patients and statistician were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described

Woo 2002

Methods	Consecutive patients undergoing cardiac surgery; block randomized with sealed envelopes; allocation concealment described in follow-up correspondence; blinding of patients done, but researchers and care givers not blinded; moderate methodological quality of study	
Participants	Elective cardiac surgery patients (with high risk of postoperative renal dysfunction). Dopamine group, n = 20, age, mean = 64.5, range 58-82; control group, n = 22, age, mean = 66.5, range 48-84)	
Interventions	Dopamine infusion 3 mcg/kg/min during operation and for 48 hrs post-operation; saline infusion for the control group	
Outcomes	Data on urine output obtained following correspondence	
Notes	Contacted the author and obtained excellent response	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were randomized'; no further details on method of randomization used
Allocation concealment (selection bias)	High risk	'Patients were randomized'; no details on method of allocation used
Blinding (performance bias and detection bias)	High risk	No details on blinding

Woo 2002 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight patients were excluded due to death or major complications
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Yavuz 2002A

Methods	Elective CABG patients; randomized, but method not described; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Elective CABG patients. Dopamine group, n = 11, age, mean = 55.7, SD = 5.2; control group, n = 11, age, mean = 56.4, SD = 9.5	
Interventions	Dopamine 2 mcg/kg/min infusion, started 24 hrs before surgery and continued for 48 hrs after surgery; control group had no treatment	
Outcomes	Creatinine clearance, free water clearance	
Notes	Contacted the author (e-mail), but no response yet	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients were prospectively randomized'; no details on method of randomization
Allocation concealment (selection bias)	High risk	'Patients were prospectively randomized'; no details on method of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States no deaths; no description of any dropouts

Yavuz 2002B

Methods	CABG patients; randomized, but method of randomization unclear; allocation concealment not used; blinding of patients, researchers and care givers is unknown; poor methodological quality study	
Participants	Elective CABG patients. Control group, n = 15, age, mean = 61.3, SD = 8.3; dopamine group, n = 15, age, mean = 58.3, SD = 5.3; diltiazem group, n = 15, age, mean = 60.3, SD = 7.1; dopamine + diltiazem group, n = 15, age, mean = 58.7, SD = 7.1 (excluded this group from review)	
Interventions	Dopamine and diltiazem 2 mcg/kg/min, started 24 hrs pre-operation and continued for 48 hrs post-operation; no mention of how control group was treated	
Outcomes	Creatinine clearance, free water clearance	

Notes	Contacted (e-mail) to author, no response yet
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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients randomized into four groups'; no further details on randomization
Allocation concealment (selection bias)	High risk	'Patients randomized into four groups'; no description of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'No mortality' is described, but not any suggestion of dropouts

Methods	CABG surgery. Randomization done, but method of randomization, allocation concealment and blinding not described. Methodological quality poor
Participants	Diltiazem infusion (2 doses): Group 1, diltiazem 1 mcg/kg/min, n = 11, age, mean = 58.1, SD = 10.7; Group 2, diltiazem 2 mcg/kg/min, n = 12, age, mean = 58.3, SD = 5.8; control group, n = 12, age, mean = 57.8, SD = 10.1
Interventions	Intervention, group 1, diltiazem 1 mcg/kg/min and group 2, diltiazem 2 mcg/kg/min, both started after chest opening, until 24 hours in ICU. Control group had no additional treatment
Outcomes	Acute renal injury, urine output, creatinine clearance
Notes	Old study, unlikely to get more data

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘Randomly assigned’; no further details of randomization
Allocation concealment (selection bias)	High risk	‘Randomly assigned’; no further details of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts described

80

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

Study	Reason for exclusion
Abe 1993	Treatment only for very short duration during surgery
Aho 2004	Not a randomized controlled trial
Amar 2001	Treatment started only after operation
Antonucci 1996	There is no control group
Baldwin 1994	Treatment started only in the postoperative period
Boldt 2000	A phase 2 trial, looking for side effects; no controls
Boldt 2006	No control group without treatment in the trial
Boodhwani 2009	Not relevant to the review
Boutros 1979	This is not a randomized controlled trial
Bove 2005	No control group without treatment in the trial
Caglikulekci 1998	Not a randomized controlled trial
Cahill 1987	Not very relevant to the review; no randomization
Caimmi 2003	The control group received active treatment with dopamine, dobutamine or frusemide; some controls started in postoperative period only
Christakis 1992	No data relevant to the review
Christenson 1995	Not a randomized controlled trial
Dementi'eva 1996	Data not relevant to the review
Feindt 1995	Data not relevant to the review
Fischer 2002	A retrospective study only
Fisher 1998	Follow up only for 12 hours
Franklin 1997	The intervention started in the postoperative period only
Frumento 2006	Postoperative study in the intensive care unit
Garwood 2003	This is an observational study, not a randomized controlled trial or controlled trial
Gatot 2004	Started in the postoperative period in the intensive care unit
Gerola 2004	Data not relevant to the review
Gilbert 2001	Not a randomized controlled study; there is only treatment and no controls
Godet 2008	No control group

Study	Reason for exclusion
Goto 1992	No control group
Grundmann 1985	This is a postoperative study
Halpenny 2001	Started the intervention only towards the end of operation and continued only for 16 hours
Hayashida 1997	Not a randomized controlled trial
Hayashida 2000	Study lasted only 6-14 hours
Hisatomi 2012	Open study, with inadequate randomization; used multiple interventions (frusamide) in both groups
Izumi 2006	Retrospective study
Izumi 2008	Most patients received other interventions such as dopamine and frusamide
Junnarkar 2003	Not a randomized controlled trial
Kulka 1993	This is a conference abstract; data published as Kulka 1996 (included)
Kumle 1999	No control groups
Kunt 2009	There were no control group patients
Kuraoka 1995	Not a randomized controlled trial
Lema 1995	This is not a randomized controlled trial or controlled trial
Lema 1998	Control group had received active treatment
Lemmer 1996	No relevant data for the review
Levy 1995	The intervention is not relevant for the review
Licker 1999	We could not exclude if this study contained the same data as in Licker 1996; hence excluded this publication from analysis
Lim 2002	Postoperative study
Loef 2002	Not a randomized controlled trial
MacGregor 1994	No control group; intervention mostly in the intensive care unit
Mahesh 2008	The follow up was only for 12 hrs
Mahmood 2007	No control group patients in the trial
Memmo 2011	Only two treatment groups, no control group
Neimark 2005	The data not relevant to the review
Nguyen 2001	Not a randomized controlled trial
Nguyen 2002	Not a randomized controlled trial

Study	Reason for exclusion
Niiya 2001	Study started in the postoperative period only
Nuutinen 1976	No randomization or controls
O'Hara 2002A	Conference abstract only; data published as O'Hara 2002 (included)
Oliver 2006	No control group
Ovrum 2004	Not a randomized controlled trial
Pain 1991	The treatment using intravenous hydration is only during the preoperative period; no randomization
Paul 1986	Randomization method inadequate; two treatments were given to the treatment groups (both dopamine and mannitol)
Pavoni 1998	Postoperative study
Petry 1992	No control group
Piper 2003	Intervention started only in intensive care unit
Plusa 1991	No control group; only 2 treatments
Priano 1993	No relevant data for the review
Prifti 2001	Study did not look at renal function
Regragui 1995	No clear intervention in the study
Riess 2000	Not a randomized controlled trial
Ryckwaert 1995	Abstract publication only; data published as Ryckwaert 2001 (included)
Sanders 2001	Study of intravenous fluid administration in the preoperative period only; no relevant data reported
Sezai 2006	Not a randomized controlled trial
Sherry 1997	Study started in intensive care unit
Skillman 1975	There is no relevant data for the review
Stanitsh 2002	Multiple measures used for the purpose of renal protection in the intervention group (mannitol + dopamine or frusemide)
Straka 2004	There is no renal data in the study
Tataranni 1994	Not a randomized controlled trial
Torsello 1993	Used only retrospective controls
Tripathy 1996	No control group
Ueki 1995	Not a randomized controlled trial

Study	Reason for exclusion
Vogt 1996	No control group
Vogt 1999	No control group
Weisz 2009	It is a group registry only and not a RCT
Welch 1993	The renal function tests were done only for very short periods of time
Wool 2010	Not relevant to the review

Characteristics of studies awaiting assessment *[ordered by study ID]*

Fergany 2011

Methods	RCT
Participants	Patients undergoing partial nephrectomy of solitary kidney
Interventions	Fenoldopam and placebo
Outcomes	
Notes	Awaiting full publication; unable to contact authors

DATA AND ANALYSES

Comparison 1. Dopamine and analogues versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	11	583	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.48, 4.73]
2 Acute renal injury	10	541	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.44, 4.23]
3 Urine output	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 24 hours (mL/min)	13	670	Mean Difference (IV, Random, 95% CI)	0.18 [-0.19, 0.54]
3.2 2 to 4 days (mL/min)	7	380	Mean Difference (IV, Random, 95% CI)	0.51 [0.04, 0.97]
3.3 5 to 7 days (mL/min)	4	103	Mean Difference (IV, Random, 95% CI)	0.23 [-0.06, 0.51]
4 Creatinine clearance	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours (mL/min)	14	616	Mean Difference (IV, Random, 95% CI)	7.17 [-5.53, 19.86]
4.2 2 to 4 days (mL/min)	9	459	Mean Difference (IV, Random, 95% CI)	7.31 [-6.19, 20.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 5 to 7 days (mL/min)	5	115	Mean Difference (IV, Random, 95% CI)	-3.33 [-13.63, 6.98]
5 Free water clearance	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 hours (mL/min)	6	166	Mean Difference (IV, Random, 95% CI)	0.03 [-0.17, 0.22]
6 Fractional excretion of sodium	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 24 hours (%)	5		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Renal plasma flow (24 hours)	2	48	Mean Difference (IV, Random, 95% CI)	75.36 [-63.27, 213.98]

Analysis 1.1. Comparison 1 Dopamine and analogues versus no intervention, Outcome 1 Mortality.

Analysis 1.2. Comparison 1 Dopamine and analogues versus no intervention, Outcome 2 Acute renal injury.

Analysis 1.3. Comparison 1 Dopamine and analogues versus no intervention, Outcome 3 Urine output.

Analysis 1.4. Comparison 1 Dopamine and analogues versus no intervention, Outcome 4 Creatinine clearance.

Analysis 1.5. Comparison 1 Dopamine and analogues versus no intervention, Outcome 5 Free water clearance.

Analysis 1.6. Comparison 1 Dopamine and analogues versus no intervention, Outcome 6 Fractional excretion of sodium.

Analysis 1.7. Comparison 1 Dopamine and analogues versus no intervention, Outcome 7 Renal plasma flow (24 hours).

Comparison 2. Diuretics versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4	255	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.49 [0.80, 7.74]
2 Acute renal injury	5	305	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.39 [0.68, 8.47]
3 Urine output	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 24 hours (mL/min)	4	141	Mean Difference (IV, Random, 95% CI)	0.10 [-0.12, 0.33]
3.2 2 to 4 days (mL/min)	2	89	Mean Difference (IV, Random, 95% CI)	0.15 [-0.14, 0.45]
4 Creatinine clearance	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours (mL/min)	3	123	Mean Difference (IV, Random, 95% CI)	-18.02 [-41.78, 5.75]
4.2 2 to 4 days (mL/min)	3	120	Mean Difference (IV, Random, 95% CI)	2.33 [-14.76, 19.42]

Analysis 2.1. Comparison 2 Diuretics versus no intervention, Outcome 1 Mortality.

Analysis 2.2. Comparison 2 Diuretics versus no intervention, Outcome 2 Acute renal injury.

Analysis 2.3. Comparison 2 Diuretics versus no intervention, Outcome 3 Urine output.

Analysis 2.4. Comparison 2 Diuretics versus no intervention, Outcome 4 Creatinine clearance.

Comparison 3. Calcium channel blockers versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	68	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Acute renal injury	6	172	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.01, 1.17]
3 Urine output	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Urine output: 24 hours (mL/min)	4	170	Mean Difference (IV, Fixed, 95% CI)	0.23 [0.02, 0.45]
4 Creatinine clearance	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours (mL/min)	5	251	Mean Difference (IV, Random, 95% CI)	4.74 [-3.30, 12.77]
4.2 2 to 4 days (mL/min)	2	130	Mean Difference (IV, Random, 95% CI)	13.92 [-24.62, 52.46]
5 Free water clearance	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 hours (mL/min)	3	91	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.47, 0.29]

Analysis 3.1. Comparison 3 Calcium channel blockers versus no intervention, Outcome 1 Mortality.

Study or subgroup	Calcium channel blockers	No intervention	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
de Lasson 1997	0/11	0/12			Not estimable
Yavuz 2002B	0/30	0/15			Not estimable
Total (95% CI)	41	27			Not estimable
Total events: 0 (Calcium channel blockers), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours [CCBlockers] 0.01 0.1 1 10 100 Favours [no intervention]

Analysis 3.2. Comparison 3 Calcium channel blockers versus no intervention, Outcome 2 Acute renal injury. **Analysis 3.3. Comparison 3 Calcium channel blockers versus no intervention, Outcome 3 Urine output.** **Analysis 3.4. Comparison 3 Calcium channel blockers versus no intervention, Outcome 4 Creatinine clearance.**

Analysis 3.5. Comparison 3 Calcium channel blockers versus no intervention, Outcome 5 Free water clearance.

Comparison 4. ACE inhibitors versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	14	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
2 Acute renal injury	3	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Renal plasma flow	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 RPF: end of operation (mL/min)	3	62	Mean Difference (IV, Random, 95% CI)	46.37 [-68.61, 161.34]

Analysis 4.1. Comparison 4 ACE inhibitors versus no intervention, Outcome 1 Mortality.

Analysis 4.2. Comparison 4 ACE inhibitors versus no intervention, Outcome 2 Acute renal injury.

Study or subgroup	ACE inhibitors n/N	No intervention n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Colson 1990	0/8	0/10			Not estimable
Colson 1992	0/18	0/8			Not estimable
Licker 1996	0/11	0/9			Not estimable
Total (95% CI)	37	27			Not estimable
Total events: 0 (ACE inhibitors), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 4.3. Comparison 4 ACE inhibitors versus no intervention, Outcome 3 Renal plasma flow.

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
4.3.1 RPF: end of operation (mL/min)							
Colson 1990	8	608.5 (387.7)	10	548.5 (487.9)		8.08%	60[-344.5,464.5]
Colson 1992	16	306.5 (190)	8	317 (172.8)		57.46%	-10.5[-162.18,141.18]
Licker 1996	11	523 (231)	9	385 (215)		34.46%	138[-57.87,333.87]
Subtotal ***	35		27			100%	46.37[-68.61,161.34]
Heterogeneity: Tau ² =0; Chi ² =1.39, df=2(P=0.5); I ² =0%							
Test for overall effect: Z=0.79(P=0.43)

Comparison 5. Atrial natriuretic peptide versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	3	825	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.19, 1.44]
2 Acute renal injury	4	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.08, 0.64]
3 Urine output at 24 hours	3	584	Mean Difference (IV, Random, 95% CI)	0.42 [0.18, 0.67]
4 Creatinine clearance, 24 hours	5	905	Mean Difference (IV, Random, 95% CI)	35.23 [-0.48, 70.94]
5 Creatinine clearance, 2 to 3 days	5	905	Mean Difference (IV, Random, 95% CI)	27.30 [4.36, 50.23]

Analysis 5.1. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 1 Mortality.

Analysis 5.2. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 2 Acute renal injury.

Analysis 5.3. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 3 Urine output at 24 hours.

Analysis 5.4. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 4 Creatinine clearance, 24 hours.

Analysis 5.5. Comparison 5 Atrial natriuretic peptide versus no intervention, Outcome 5 Creatinine clearance, 2 to 3 days.

Comparison 6. N-Acetyl cysteine versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.42, 2.42]
2 Acute renal injury	5	601	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.32, 2.62]
3 Urine output, 24 hours	2	146	Mean Difference (IV, Random, 95% CI)	0.18 [-0.24, 0.60]

Analysis 6.1. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 1 Mortality.

Analysis 6.2. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 2 Acute renal injury.

Analysis 6.3. Comparison 6 N-Acetyl cysteine versus no intervention, Outcome 3 Urine output, 24 hours.

Comparison 7. Erythropoietin (EPO) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.63]
2 Acute renal injury	1	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Urine output: 24 hours	1	71	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.47, 0.21]
4 Urine output: 2 to 3 days	1	71	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.56, 0.18]
5 Urine output: 5 to 7 days	1	71	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.50, 0.22]

Analysis 7.1. Comparison 7 Erythropoietin (EPO) versus control, Outcome 1 Mortality.

Analysis 7.2. Comparison 7 Erythropoietin (EPO) versus control, Outcome 2 Acute renal injury.

Analysis 7.3. Comparison 7 Erythropoietin (EPO) versus control, Outcome 3 Urine output: 24 hours.

Analysis 7.4. Comparison 7 Erythropoietin (EPO) versus control, Outcome 4 Urine output: 2 to 3 days.

Analysis 7.5. Comparison 7 Erythropoietin (EPO) versus control, Outcome 5 Urine output: 5 to 7 days.

Comparison 8. Intravenous fluid versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4	152	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.16, 3.42]
2 Acute renal injury	3	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.05, 0.96]
3 Creatinine clearance	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 24 hours (mL/min)	2	77	Mean Difference (IV, Random, 95% CI)	-10.34 [-29.57, 8.88]

Analysis 8.1. Comparison 8 Intravenous fluid versus control, Outcome 1 Mortality.

Analysis 8.2. Comparison 8 Intravenous fluid versus control, Outcome 2 Acute renal injury.

Analysis 8.3. Comparison 8 Intravenous fluid versus control, Outcome 3 Creatinine clearance.

Comparison 9. Cardiac surgery: subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	26	2390	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.56, 1.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Acute renal injury	31	2504	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.32, 0.92]
3 Urine output	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 24 hours (mL/min)	17	1475	Mean Difference (IV, Random, 95% CI)	0.26 [0.17, 0.36]
3.2 2 to 3 days (mL/min)	9	1058	Mean Difference (IV, Random, 95% CI)	0.21 [-0.13, 0.54]
4 Creatinine clearance	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours (mL/min)	24	2136	Mean Difference (IV, Random, 95% CI)	9.38 [-5.99, 24.74]
4.2 2 to 3 days (mL/min)	17	1844	Mean Difference (IV, Random, 95% CI)	14.21 [3.58, 24.85]
4.3 5 to 7 days (mL/min)	7	949	Mean Difference (IV, Random, 95% CI)	14.99 [0.84, 29.13]
5 Free water clearance	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 hours (mL/min)	7	700	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.22, 0.19]
5.2 2 to 3 days (mL/min)	4	591	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.30, -0.28]
6 Fractional excretion of sodium	9		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 24 hours (%)	8		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 2 to 4 days (%)	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 1 Mortality.

Analysis 9.2. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 2 Acute renal injury.

Analysis 9.3. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 3 Urine output.

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for overall effect: $Z=1.19(P=0.23)$

Favours control -10 -5 0 5 10 Favours treatment

Analysis 9.4. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 4 Creatinine clearance.

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

9.4.1 24 hours (mL/min)

Amano 1994	10	92 (12.8)	9	64.2 (12.8)	+	4.6%	27.8[16.27,39.33]
Amano 1995	13	73.3 (24.2)	10	77.7 (13.9)	+	4.5%	-4.4[-20.11,11.31]
Ascione 1999	25	87.3 (5.2)	26	71.7 (3.9)	+	4.71%	15.6[13.07,18.13]
Berendes 1997	30	124.7 (9.5)	14	88 (6.6)	+	4.7%	36.7[31.85,41.55]
Carcoana 2003	51	88.3 (28.1)	24	93.6 (34.4)	+	4.49%	-5.3[-21.08,10.48]
Chen 2007	17	44.8 (4.4)	19	43.9 (2.8)	+	4.71%	0.9[-1.54,3.34]
Cogliati 2007	95	68.1 (14.3)	98	38.6 (9.2)	+	4.71%	29.5[26.1,32.9]
Costa 1990	24	66.3 (66.1)	12	78.5 (35.3)	+	3.87%	-12.2[-45.34,20.94]
Dehne 2001	24	55.3 (10.9)	24	54.7 (10.5)	+	4.68%	0.6[-5.46,6.66]
Donmez 1998	50	91.3 (70.5)	25	107.2 (44.5)	+	4.15%	-15.95[-42.14,10.24]
Kaya 2007	124	73.3 (17.3)	116	66.7 (15.8)	+	4.7%	6.6[2.41,10.79]
Kleinschmidt 1997	27	172 (70.5)	13	179 (80)	+	3.11%	-7[-57.97,43.97]
Kramer 2002	28	102.8 (76.7)	28	101.2 (71.8)	+	3.62%	1.6[-37.31,40.51]
Kulka 1996	23	91 (16)	25	69 (18)	+	4.63%	22[12.38,31.62]
Lassnigg 2000	42	94.5 (52)	40	112 (56)	+	4.25%	-17.5[-40.92,5.92]
Morgera 2002	17	103.3 (39.2)	17	67.8 (39.2)	+	4.14%	35.5[9.15,61.85]
Myles 1993	25	91.2 (78)	24	107 (72)	+	3.49%	-15.8[-57.81,26.21]
Prasad 2010	35	80 (27)	35	77 (27)	+	4.57%	3[-9.65,15.65]
Sezai 2000	20	120.9 (77.6)	20	40.3 (8.9)	+	3.82%	80.6[46.37,114.83]
Sezai 2009	251	128.9 (4.5)	253	66.2 (3.6)	+	4.72%	62.7[61.99,63.41]
Sezai 2011	141	46.3 (1.3)	144	41.2 (1.2)	+	4.72%	5.1[4.81,5.39]
Urzua 1992	7	102 (27.2)	14	136 (91.8)	+	3.06%	-34[-86.14,18.14]
Yavuz 2002A	11	49.9 (65.2)	11	67 (80.9)	+	2.69%	-17.1[-78.5,44.3]
Yavuz 2002B	30	53.8 (56.7)	15	69 (79.1)	+	3.36%	-15.2[-60.08,29.68]
Subtotal ***	1120		1016		◆	100%	9.38[-5.99,24.74]

Heterogeneity: $\tau^2=1302.64$; $\chi^2=21926.76$, $df=23(P<0.0001)$; $I^2=99.9\%$
Test for overall effect: $Z=1.2(P=0.23)$

9.4.2 2 to 3 days (mL/min)

Amano 1994	10	107 (12.8)	9	72.8 (8.6)	+	6.5%	34.2[24.48,43.92]
Ascione 1999	25	83.4 (6.5)	26	70.4 (5.2)	+	6.83%	13[9.76,16.24]
Barr 2008	39	33.8 (2.1)	19	26.6 (2.2)	+	6.87%	7.2[6.01,8.39]
Chen 2007	17	44.3 (3.3)	19	38.7 (2.8)	+	6.86%	5.6[3.59,7.61]
Cogliati 2007	95	65.4 (18.4)	98	33.7 (11.2)	+	6.8%	31.7[27.39,36.01]
Kaya 2007	124	67 (15.4)	116	61.1 (15.1)	+	6.82%	5.9[2.04,9.76]
Kramer 2002	28	100.4 (80.8)	28	96.3 (68.6)	+	3.55%	4.1[-35.16,43.36]
Kulka 1996	23	85.3 (27.3)	25	78.4 (27.3)	+	6.01%	6.9[-8.56,22.36]
Lassnigg 2000	83	84 (52.5)	40	95 (54)	+	5.51%	-11[-31.19,9.19]
Loef 2004	10	88.5 (7.5)	10	100.7 (10.3)	+	6.63%	-12.2[-20.1,-4.3]
Morgera 2002	17	108.1 (39.2)	17	86.6 (39.2)	+	4.84%	21.5[-4.85,47.85]
Prasad 2010	35	80 (31)	35	76 (28)	+	6.16%	4[-9.84,17.84]

Favours control -400 -200 0 200 400 Favours treatment

Analysis 9.5. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 5 Free water clearance.

Analysis 9.6. Comparison 9 Cardiac surgery: subgroup analysis, Outcome 6 Fractional excretion of sodium.

Comparison 10. Aortic surgery: subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	8	236	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.20, 2.89]
2 Acute renal injury	8	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.11, 3.70]
3 Urine output	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 24 hours (mL/min)	7	227	Mean Difference (IV, Random, 95% CI)	0.04 [-0.10, 0.19]
3.2 2 to 3 days (mL/min)	3	95	Mean Difference (IV, Random, 95% CI)	0.26 [-0.06, 0.58]
3.3 5 to 7 days (mL/min)	2	55	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.39, 0.21]
4 Creatinine clearance	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours (mL/min)	9	323	Mean Difference (IV, Random, 95% CI)	7.99 [-0.77, 16.74]
4.2 2 to 3 days (mL/min)	5	195	Mean Difference (IV, Random, 95% CI)	11.62 [-6.13, 29.37]
4.3 5 to 7 days (mL/min)	4	116	Mean Difference (IV, Random, 95% CI)	-12.85 [-26.41, 0.72]
5 Free water clearance	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 hours (mL/min)	5	154	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.51, 0.01]
5.2 2 to 4 days (mL/min)	2	85	Mean Difference (IV, Random, 95% CI)	0.37 [-0.12, 0.85]
5.3 5 to 7 days (mL/min)	2	85	Mean Difference (IV, Random, 95% CI)	0.24 [-0.13, 0.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Fractional excretion of sodium	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 24 hours (%)	5		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 2 to 4 days (%)	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Renal plasma flow	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 End of operation (mL/min)	2	44	Mean Difference (IV, Random, 95% CI)	50.29 [-92.83, 193.40]
7.2 24 hours (mL/min)	2	47	Mean Difference (IV, Random, 95% CI)	45.86 [-18.64, 110.36]

Analysis 10.1. Comparison 10 Aortic surgery: subgroup analysis, Outcome 1 Mortality.

Analysis 10.2. Comparison 10 Aortic surgery: subgroup analysis, Outcome 2 Acute renal injury.

Study or subgroup	Interventions n/N	No intervention n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total events: 2 (Interventions), 3 (No intervention)					
Heterogeneity: $\tau^2=0$; $\chi^2=0.89$, $df=2$ ($P=0.64$); $I^2=0\%$					
Test for overall effect: $Z=0.52$ ($P=0.6$)

Analysis 10.3. Comparison 10 Aortic surgery: subgroup analysis, Outcome 3 Urine output.

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
10.3.1 24 hours (mL/min)							
Dawidson 1991	10	1.2 (0.5)	10	1.3 (0.7)		7.54%	-0.09[-0.62,0.44]
Nicholson 1996	15	1.6 (0.6)	13	1.2 (0.6)		12.22%	0.33[-0.09,0.75]
Licker 1996	11	1.6 (0.6)	9	1.5 (0.3)		13.06%	0.1[-0.31,0.51]
de Lasson 1997	11	1.3 (1.3)	12	1.4 (1.3)		1.84%	-0.12[-1.2,0.96]
Halpenny 2002	14	1.2 (0.5)	13	1.2 (0.6)		12.25%	0[-0.42,0.42]
Hynninen 2006	34	1.6 (0.4)	35	1.6 (0.4)		52.07%	0[-0.2,0.2]
Mitaka 2008	20	4.8 (2)	20	4.8 (2.6)		1.01%	0[-1.46,1.46]
Subtotal ***	115		112			100%	0.04[-0.1,0.19]
Heterogeneity: $\tau^2=0$; $\chi^2=2.42$, $df=6$ ($P=0.88$); $I^2=0\%$							
Test for overall effect: $Z=0.59$ ($P=0.55$)							
10.3.2 2 to 3 days (mL/min)							
Nicholson 1996	15	1.2 (0.6)	13	1.2 (0.6)		48.72%	0.03[-0.39,0.45]
Halpenny 2002	14	1.7 (0.7)	13	1.2 (0.5)		42.8%	0.5[0.04,0.96]
Mitaka 2008	20	4.6 (1.9)	20	4.2 (1.7)		8.48%	0.36[-0.74,1.46]
Subtotal ***	49		46			100%	0.26[-0.06,0.58]
Heterogeneity: $\tau^2=0.01$; $\chi^2=2.23$, $df=2$ ($P=0.33$); $I^2=10.37\%$							
Test for overall effect: $Z=1.57$ ($P=0.12$)							
10.3.3 5 to 7 days (mL/min)							
Nicholson 1996	15	1.1 (0.4)	13	1.1 (0.4)		65.86%	0.02[-0.28,0.32]
Halpenny 2002	14	1.5 (0.5)	13	1.8 (0.7)		34.14%	-0.3[-0.76,0.16]
Subtotal ***	29		26			100%	-0.09[-0.39,0.21]
Heterogeneity: $\tau^2=0.01$; $\chi^2=1.3$, $df=1$ ($P=0.25$); $I^2=23.23\%$							
Test for overall effect: $Z=0.59$ ($P=0.56$)

Analysis 10.4. Comparison 10 Aortic surgery: subgroup analysis, Outcome 4 Creatinine clearance.

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
10.4.1 24 hours (mL/min)							
Shackford 1983	30	72 (43.8)	28	81 (47.6)		10.73%	-9[-32.59,14.59]
Pull Ter Gunne 1990	8	72 (36)	11	85 (37)		6.09%	-13[-46.17,20.17]
de Lasson 1995	12	81.5 (28.6)	12	78.9 (35.4)		9.35%	2.55[-23.18,28.28]
Nicholson 1996	15	57.6 (41.4)	13	63.6 (36.8)		7.69%	-6[-34.97,22.97]
Licker 1996	11	88 (23)	9	64 (22)		13.96%	24[4.22,43.78]

Analysis 10.5. Comparison 10 Aortic surgery: subgroup analysis, Outcome 5 Free water clearance.

Analysis 10.6. Comparison 10 Aortic surgery: subgroup analysis, Outcome 6 Fractional excretion of sodium.

Analysis 10.7. Comparison 10 Aortic surgery: subgroup analysis, Outcome 7 Renal plasma flow.

Comparison 11. Biliary surgery: subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urine output	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Urine output: 24 hours (mL/min)	2	43	Mean Difference (IV, Random, 95% CI)	-0.59 [-0.99, -0.19]
1.2 Urine output: 2 to 4 days (mL/min)	2	43	Mean Difference (IV, Random, 95% CI)	0.24 [-0.22, 0.69]
1.3 Urine output: 5 to 7 days (mL/min)	2	43	Mean Difference (IV, Random, 95% CI)	0.23 [0.09, 0.37]
2 Creatinine clearance	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 24 hours (mL/min)	3	83	Mean Difference (IV, Random, 95% CI)	-2.84 [-14.07, 8.39]
2.2 2 to 4 days (mL/min)	3	74	Mean Difference (IV, Random, 95% CI)	0.42 [-16.68, 17.52]
2.3 5 to 7 days (mL/min)	2	43	Mean Difference (IV, Random, 95% CI)	0.58 [-16.43, 17.60]

Analysis 11.1. Comparison 11 Biliary surgery: subgroup analysis, Outcome 1 Urine output.

Analysis 11.2. Comparison 11 Biliary surgery: subgroup analysis, Outcome 2 Creatinine clearance.

Comparison 12. Studies on participants with pre-existing renal impairment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	10	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.36, 1.52]
2 Acute renal injury	11	979	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.22, 0.76]
3 Urine output	4	707	Mean Difference (IV, Random, 95% CI)	0.35 [-0.16, 0.85]
3.1 Urine output, 24 hours	4	416	Mean Difference (IV, Random, 95% CI)	0.35 [-0.12, 0.81]
3.2 Urine output, 2 to 3 days	2	291	Mean Difference (IV, Random, 95% CI)	0.43 [-0.78, 1.65]
4 Creatinine clearance	4	646	Mean Difference (IV, Random, 95% CI)	10.65 [0.04, 21.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Creatinine clearance, 24 hours	4	347	Mean Difference (IV, Random, 95% CI)	7.78 [-10.39, 25.94]
4.2 Creatinine clearance, 2 to 3 days	3	299	Mean Difference (IV, Random, 95% CI)	14.16 [-6.20, 34.52]

Analysis 12.1. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 1 Mortality.

Analysis 12.2. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 2 Acute renal injury.

Analysis 12.3. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 3 Urine output.

Analysis 12.4. Comparison 12 Studies on participants with pre-existing renal impairment, Outcome 4 Creatinine clearance.

Comparison 13. Studies with low risk of bias: sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reported mortality, low risk of bias studies only	19	1604	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.52, 1.97]
2 Acute renal injury, requiring dialysis, low risk of bias studies only	16	1550	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.55, 2.03]
3 Urine output at 24 hours, low risk of bias studies only	11	798	Mean Difference (IV, Random, 95% CI)	0.20 [-0.04, 0.44]
4 Creatinine clearance at 24 hours, low risk of bias studies only	9	817	Mean Difference (IV, Random, 95% CI)	6.59 [-3.53, 16.72]

Analysis 13.1. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 1 Reported mortality, low risk of bias studies only.

Analysis 13.2. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 2 Acute renal injury, requiring dialysis, low risk of bias studies only.

Analysis 13.3. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 3 Urine output at 24 hours, low risk of bias studies only.

Analysis 13.4. Comparison 13 Studies with low risk of bias: sensitivity analysis, Outcome 4 Creatinine clearance at 24 hours, low risk of bias studies only.

ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study ID	Randomization	Allocation concealment	Blinding	With- drawals recorded	Overall quality
Adabag 2008	Randomly as- signed by the investigational pharmacist	Participants, researchers and clini- cians blinded to treatment assign- ment	Participants, researchers and clinicians (including data col- lecting nurse) blinded	Not report- ed	Good

Table 1. Methodological quality of included studies (Continued)

	Block randomization (blocks of 10)		Drug packets matched in volume, colour, consistency and transparency and given mixed with fruit juice to mask taste		
Amano 1994	'Randomly assigned' into two groups	None described	None described; control group had no treatment	Not described	Poor
Amano 1995	'Patients were randomized into either diltiazem or no treatment'	Not described	None described; control group had no treatment	Not described	Poor
Ascione 1999	'Prospectively randomized by card allocation'	'Prospectively randomized by card allocation'	Not used	Not discussed	Moderate
Barr 2008	Randomization done by pharmacy department; method of randomization uncertain Not sure about adequacy of randomization	No specific mention of allocation concealment except to say 'double-blinded' Allocation concealment inadequate	No specific mention of who all were blinded; 'double-blinded', placebo-controlled trial Not sure whether blinding was adequate	One withdrawal from study reported	Moderate
Berendes 1997	'Placebo controlled prospective study'; no randomization	None described	None described	Not described	Poor
Bergman 2002	'Consented and were randomized'	Not described	Not used	3 participants (2, 1) not operated upon; 2 participants excluded from final analysis because of clinical management changes	Poor
Burns 2005	Randomization done by pharmacy trial co-ordinator using a permitted block strategy	Allocation concealment using central randomization with drugs prepared by pharmacy	Quadruple-blinded (participants, clinicians, data collectors and data analyst) placebo-controlled study	Clearly accounted for (5 in intervention group and 2 in control group)	Good
Carcoana 2003	'Prospective randomized double-blinded and	Not specifically described, but quite likely it was concealed allocation	Blinded manner; drug or saline supplied by the department investigational pharmacy in a	All allocated participants com-	Good

Table 1. Methodological quality of included studies (Continued)

	placebo-controlled study'		blinded manner + additive for the CPB circuit prime (mannitol or saline, supplied similarly)	pleted the trial (withdrawals before allocation)	
	Computer-generated random number tables				
Chen 2007	'Randomized'; no details provided 'Double-blind, placebo-controlled proof of concept trial'	No details provided 'Double-blind, placebo-controlled proof of concept trial'	No details provided 'Double-blind, placebo-controlled proof of concept trial'	Four withdrawals from trial reported	Poor
Cho 2009	Computer-generated randomization method used	Computer allocation, no further details given	Not described except by the statement, 'investigator blinded to the study group evaluated the postoperative data'	Not reported	Moderate
Cogliati 2007	Randomization from a computer list, in an envelope	Sealed envelope used 'All personnel and patients were blinded to the assignment'	Blinded nurse, not involved with study, prepared the drug/placebo in identical 50 mL filled syringes 'All personnel and patients were blinded to the assignment'	1 participant	Good
Colson 1990	Allocated in a randomized double-blind fashion to 2 groups No details on randomization method	Allocated in a randomized double-blind fashion to 2 groups No description of allocation concealment	No details on blinding except 'double-blind fashion'	Not given	Poor
Colson 1992	Allocated in a randomized double-blind fashion to 2 groups No details on randomization method	Allocated in a randomized double-blind fashion to 2 groups No description of allocation concealment	No details on blinding except 'double-blind fashion'	Not given	Poor
Costa 1990	Participants with renal dysfunction (CCI < 50 mL/min) 'Randomly divided into 3 groups'; no description of randomization	No description of allocation	No description of blinding	Not given	Poor
Cregg 1999	'Randomly allocated' into 3 groups; no de-	No description of allocation	No description of blinding	Not given	Poor

Table 1. Methodological quality of included studies (Continued)

scription of randomization					
Dawidson 1991	'Randomized to either treatment group' by pulling a card from a previously prepared deck	No description of allocation concealment	No details on blinding	Not given	Poor
de Lasson 1995	'Randomly allocated into infusion of dopamine or placebo' by one of the authors, who was unaware of the treatment allocation	'Randomly allocated into infusion of dopamine or placebo' by one of the authors, who was unaware of the treatment allocation; no description of allocation concealment	No blinding described	Not given	Poor
de Lasson 1997	Randomization and drug or placebo preparation provided by drug company; method not described, but likely to be good	Not sure of any allocation concealment, but likely possible	Possible, but blinded tables not described	1 participant had additional drugs but was not excluded	Moderate
Dehne 2001	Randomly allocated into 2 groups, randomization method not described	Allocation concealment not described	Blinding not mentioned	All participants accounted for in calculations	Poor
Donmez 1998	'Randomly allocated into 3 groups'; method of randomization not described	'Randomly allocated into 3 groups'; method of allocation concealment not described	'Randomly allocated into 3 groups'; method of blinding not described	Dropouts not described	Poor
Dural 2000	'Randomly allocated into 3 groups'; method of randomization not described	'Randomly allocated into 3 groups'; method of allocation concealment not described	'Randomly allocated into 3 groups'; method of blinding not described	Dropouts not described	Poor
Durmaz 2003	Randomization done by the last digit of the medical record number of participant (quasi-randomization)	'Patients were prospectively allocated into 2 groups' No details given	Not given	Not given	Poor

Table 1. Methodological quality of included studies (Continued)

Fischer 2005	Retrospective chart review of a randomized trial in 2003, which used computer-generated allocation list (randomly permuted blocks of random size) provided by department of Medical Statistics	Computer-generated allocation list (randomly permuted blocks of random size) provided by department of Medical Statistics	Drugs supplied in identical looking glass vials containing drug or placebo	Exclusions described in text	Good
Gubern 1988	'Prospectively randomized'; no details of method of randomization	'Prospectively randomized'; no details of method of allocation	'Prospectively randomized'; no details of method of blinding	Fate of participants discussed	Poor
Haase 2007	Random assignment of participants using Microsoft Excel-based random number generation to create a randomization list, in blocks of 10	Allocation concealment ensured by quadruple-blinding (participants, clinicians, data collectors and data analysers were unaware of groups or treatment)	Quadruple-blinding (participants, clinicians, data collectors and data analysers were blinded)	0 participants	Good
Haase 2009	Microsoft Excel-based random number generation, with blocks of 10; central randomization by department of pharmacy	Allocation concealment achieved by central randomization, blinding to all researchers, participants and others. Allocation revealed only after data analysis	Both fluids in separate shrink-wrapped black plastic bags that were identical in appearance (blinded to participants, anaesthetists, surgeons, ICU personnel, nurses and others)	1 in each group	Good
Halpeny 2002	'Random allocation used'; method not given	'Random allocation used'; method not given	'Random allocation used'; method not given	1 participant excluded from the trial	Poor
Harten 2008	'Randomized', but no details given	Allocated to control and intervention groups using opaque envelopes immediately before surgery; not sure whether allocation was maintained	No blinding	1 died before operation (intervention group)	Poor
Hynninen 2006	Random assignment in blocks of 10 done by hospital pharmacy, no details given	Allocation done by hospital pharmacy Clinical and study personnel not aware of study allocation	Blinding quite likely, although not detailed in text	1 participant withdrew from study intra-operatively	Moderate

Table 1. Methodological quality of included studies (Continued)

				(does not mention which group, although most likely the intervention group—1 less in that group)	
Kaya 2007	Computer-generated randomization done by statistician	Sequentially numbered, sealed envelopes	SNP and saline in uniformly appearing 50 mL syringes, blinded to surgeons, perfusionists and nurses; investigators did not know the details	None	Good
Klein-schmidt 1997	Randomization by computer	Not described in detail	Not described in detail	No detailed description	Poor
Kramer 2002	Participants randomly assigned to receive 1 of 2 treatments	No details given	No details given	Early termination of study in 33 of 56 participants; ITT used	Poor
Kulka 1996	Allocated into 2 groups in a double-blinded random fashion; no details of randomization given	Allocated into 2 groups in a double-blinded random fashion; no details of allocation given	Allocated into 2 groups in a double-blinded random fashion; no details of blinding given	2 participants excluded	Poor
Lassnigg 2000	Placebo-controlled randomized double-blind trial; block randomization done and sealed envelopes used	Placebo-controlled randomized double-blind trial; block randomizations done with the use of sealed envelopes; no further details on allocation concealment provided	Placebo-controlled randomized double-blind trial; no other details of blinding provided	3 participants excluded from analysis	Moderate
Lau 2001	'Recruited patients were allocated to one of 2 groups'; no details on randomization	'Recruited patients were allocated to one of 2 groups'; no details on allocation concealment	'Recruited patients were allocated to one of 2 groups'; no details on blinding provided	2 participants accounted for	Poor
Licker 1996	'Patients were allocated in a randomized double-blind manner'; no details of randomization given	'Patients were allocated in a randomized double-blind manner'; no details of allocation concealment given	'Patients were allocated in a randomized double-blind manner'; no details of blinding given	2 participants excluded from the trial	Poor

Table 1. Methodological quality of included studies (Continued)

Loef 2004	'Randomized in a double-blind fashion'; no details of randomization given	'Randomized in a double-blind fashion'; no details of allocation given	'Randomized in a double-blind fashion'; no details of blinding given	All participants completed the trial	Poor
Marathias 2006	Used a 2:1 ratio in randomization process, participants randomly assigned into groups; no other details of randomization given	Participants randomly assigned into groups; no other details of allocation given	Participants randomly assigned into groups; no other details of blinding given	Not given	Poor
Mitaka 2008	'Patients were randomized into 2 groups'; not sure what method of randomization was used	Not sure how allocation was performed	'Blind infusion was performed'; not sure about blinding	None indicated	Poor
Morariu 2005	Designed as a prospective double-blind placebo-controlled randomized trial; no other details of randomization provided	Prospective double-blind placebo-controlled randomized trial; no other details of allocation concealment provided	Prospective double-blind placebo-controlled randomized trial; no other details of blinding provided	All participants completed the trial	Poor
Morgera 2002	'Patients were randomized'; no other details given	'Patients were randomized'; no other details given	'Patients were randomized'; no other details given	2 participants excluded from analysis	Poor
Myles 1993	Randomly assigned with the use of a table of random numbers; 'prospective double-blind randomized trial'	Coded 50 mL syringes from the pharmacy, with contents remaining unknown to investigators until the end of the trial; allocation concealed	Coded 50 mL syringes from the pharmacy, with contents remaining unknown to investigators until the end of the trial; blinded	3 withdrawals before start of trial	Good
Nicholson 1996	'Prospective randomized trial'; no further details on randomization	'Prospective randomized trial'; no further details on allocation	'Prospective randomized trial'; no details on blinding	None reported	Poor
Nouri-Majalan 2009	'Patients were randomized'; no further details	No indication of allocation concealment, but for statement, 'To prevent bias, surgeons, nurses, and lab technicians were blinded to patient assignment'	Possible: 'To prevent bias, surgeons, nurses, and lab technicians were blinded to patient assignment'	None indicated in text	Poor

Table 1. Methodological quality of included studies (Continued)

O'Hara 2002	'Prospective randomized study'; no further details on randomization given	'Prospective randomized study'; no further details on allocation	'Prospective randomized study'; no further details on blinding	11 of 35 excluded	Poor
Parks 1994	'Patients were randomly allocated into 2 groups'; no further details on randomization	'Patients were randomly allocated into 2 groups'; no further details on allocation	'Patients were randomly allocated into 2 groups'; no further details on blinding	Not disclosed	Poor
Perez 2002	Randomization performed by aleatorized numbers prepared in closed envelopes	No details on concealment of allocation except 'Randomization performed by aleatorized numbers prepared in closed envelopes'	Drug or placebo given with an identical container in a double-blind manner with the same volume of drug or saline	4 participants excluded	Moderate
Prasad 2010	Randomized, prospective, open-label study Random number generated from a random number table	No concealment of assignment	No blinding	4 excluded after randomization?	Poor
Prowle 2012	Random assignment by the hospital pharmacy clinical trials coordinator Microsoft Excel-based random number generator permuted block strategy with blocks of 10	Allocation stratified into 2 groups based on pre-op use of statins Allocation concealed to participants, anaesthetists, cardiac surgeons, intensive care specialists, bedside nurses and investigators	'Double-blind'. Atorvastatin or placebo medication prepared in capsules of identical appearance	8 in intervention group and 7 in control group	Good
Pull Ter Gunne 1990	Random assignment into 2 groups; no further details	Random assignment into 2 groups; no further details	Random assignment into 2 groups; no further details; the anaesthesiologist was aware of the allocation and treatment received	No details provided	Poor
Ris- tikankare 2006	'Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications'	'Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications', but no details of allocation concealment provided	'Randomly allocated in a double-blinded manner; the hospital pharmacy performed the randomization and prepared the study medications'; no details of blinding provided	3 participants excluded	Moderate

Table 1. Methodological quality of included studies (Continued)

Ryckwaert 2001	'Patients were allocated in a randomized double-blind fashion to 2 groups'; no further details of randomization given	'Patients were allocated in a randomized double-blind fashion to 2 groups'; no further details of allocation given	'Patients were allocated in a randomized double-blind fashion to 2 groups'; no further details of blinding given	No dropouts detailed in text	Poor
Sezai 2000	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; no other details on randomization method	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; no other details on allocation method	'Randomly allocated to two groups receiving blind infusion of drug or placebo'; no other details on blinding	Not described, but study probably had no dropouts	Poor
Sezai 2009	Randomly allocated into 2 groups by drawing lots	'Randomly allocated by drawing lots' No other details	No evidence of blinding	No mention in the text	Poor
Sezai 2011	Randomly allocated into 2 groups by lottery method	'Randomly allocated into 2 groups'; no evidence of concealment of allocation	No blinding discussed	Dropouts discussed	Poor
Shackford 1983	Participants were assigned by random number to 1 of 2 groups; no details on randomization given	Participants were assigned by random number to 1 of 2 groups; no details on concealment of allocation given	Participants assigned by random number to 1 of 2 groups; no details on blinding	No dropouts	Poor
Shim 2007	Participants randomly allocated to 1 of 2 groups with use of a computer-generated randomization table	Participants randomly allocated to 1 of 2 groups with use of a computer-generated randomization table; no further details on allocation concealment given	All medical personnel involved in the study blinded to the contents of the infusion bottle	No dropouts recorded	Moderate
Song 2009	Block randomization developed by research centre Randomization stratified by serum creatinine levels	Allocation via Internet using predetermined randomization	Participants, healthcare clinicians and researchers blinded	None	Good
Tang 1999	Prospectively randomly assigned	No details on allocation provided in text	No details of blinding provided in text	No dropouts recorded	Poor
Tang 2002	Participants randomly assigned; no further details	Participants randomly assigned; no further details on allocation given	2 different types of procedures; no blinding possible	5 participants subsequently	Poor

Table 1. Methodological quality of included studies (Continued)

	on randomiza- tion given			excluded from trial	
Thompson 1986	'Patients were randomized'; no more details	'Patients were randomized'; no more details	No details provided	'There were no withdrawals'	Poor
Turner 2008	Random assignment done with use of computer-generated randomization list	Computer-generated randomization list placed in sealed envelopes and opened in numerical order by a third party, who prepared the study infusion	Third party prepared the infusion. Infusions were such that volumes were equal in the bag and of identical colour, and contents of the bag were indistinguishable; the infusion was done over 30 minutes to avoid haemodynamic effects of treatment	Yes, none lost	Good
Urzua 1992	Participants randomly assigned into 1 of 2 groups, according to the last digit of their clinical history number (quasi-randomization)	No description of concealment of allocation	No report of blinding	All participants completed	Poor
Wahbah 2000	'Patients were randomly allocated into 4 equal groups'; no further details on randomization	Patients were randomly allocated into 4 equal groups'; no further details on allocation	No description of blinding	None described	Poor
Welch 1995	'Patients were randomly assigned'; no further details on randomization method used	'Patients were randomly assigned'; no further details on allocation method used	No description of blinding	None described	Poor
Wijnen 2002	'Patients were randomized'; no further details on method of randomization used	'Patients were randomized'; no details on method of allocation used	No details on blinding	One death described	Poor
Witczak 2008	Participants were 'randomized' It appears that the anaesthesiologist 'randomly drew an envelope with the assigned treatment'	Allocation concealment was possible only for participants and the statistician	No; control received no treatment Participants and the statistician were blinded	Not described	Poor

Table 1. Methodological quality of included studies (Continued)

Woo 2002	'Patients were randomized'; no further details on method of randomization used	'Patients were randomized'; no details on method of allocation used	No details on blinding	8 participants excluded because of death or major complications	Poor
Yavuz 2002A	'Patients were prospectively randomized'; no details on method of randomization used	'Patients were prospectively randomized'; no details on method of allocation used	No description of blinding	States no deaths; no description of dropouts	Poor
Yavuz 2002B	'Patients randomized into 4 groups'; no further details on randomization given	'Patients randomized into 4 groups'; no description of allocation used	No description of blinding	No mortality described, but no suggestion of dropouts	Poor
Zanardo 1993	'Randomly assigned'; no further details of randomization given	'Randomly assigned'; no further details of allocation given	No blinding described	No dropouts described	Poor

APPENDICES

Appendix 1. Search strategies employed

Search strategy for MEDLINE (Ovid SP)

1 exp Kidney Failure/ or exp Kidney Failure Acute/ or exp Kidney Failure Chronic/ or exp Kidney Function Tests/ or exp Glomerular Filtration Rate/ or exp Renal Circulation/ or exp Renal Plasma Flow/ or exp Renal Insufficiency/ or kidney.ti,ab. or (glomerul* adj3 filtration).mp. or (renal adj3 (failure or protect* or function*)).mp. or kidney function test*.mp. or renal function test*.mp. or free water clearance.mp. or fractional excretion of sodium.mp. or (urine adj3 (output or flow)).mp.

2 exp Angiotensin Converting Enzyme Inhibitors/ or exp Fluid Therapy/ or exp Infusions Intravenous/ or exp Angiotensin Converting Enzyme Inhibitors/ or exp diuretics/ or exp mannitol/ or exp Furosemide/ or exp Dopamine/ or exp Dopamine Agonists/ or (diuretic* or mannitol or frusemide or furosemide).mp. or (fluid* adj3 therap*).mp. or (intravenous adj3 fluid*).mp. or hydration.ti,ab. or angiotensin converting enzyme inhibitor*.mp. or ACE inhibitor*.mp. or dopamin*.ti,ab.

3 exp Perioperative Care/ or exp Intraoperative Period/ or exp Intraoperative Care/ or exp Intraoperative Complications/ or (peri?operativ* or intra?operativ*).ti,ab.

4 1 and 2 and 3

5 reno?protect*.af.

6 4 or 5 (2513)

7 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

8 6 and 7

Search strategy for EMBASE (Ovid SP)

1 exp kidney failure/ or exp kidney failure/ or exp kidney function test/ or exp glomerulus filtration rate/ or exp kidney circulation/ or exp kidney clearance/ or exp kidney plasma flow/ or exp urine flow rate/ or exp urine volume/ or kidney.ti,ab. or (glomerul* adj3 filtration).mp. or (renal adj3 (failure or protect* or function*)).mp. or kidney function test*.mp. or renal function test*.mp. or free water clearance.mp. or fractional excretion of sodium.mp. or (urine adj3 (output or flow)).mp.

2 exp dipeptidyl carboxypeptidase inhibitor/ or exp fluid therapy/ or intravenous drug administration/ or exp diuretic agent/ or exp diuretic agent/ or exp mannitol/ or exp furosemide/ or exp dopamine/ or exp dopamine receptor stimulating agent/ or (diuretic* or mannitol or frusemide or furosemide).mp. or (fluid* adj3 therap*).mp. or (intravenous adj3 fluid*).mp. or hydration.ti,ab. or angiotensin converting enzyme inhibitor*.mp. or ACE inhibitor*.mp. or dopamin*.ti,ab.
3 exp perioperative period/ or exp intraoperative period/ or exp peroperative care/ or (peri?operativ* or intra?operativ*).ti,ab.
4 1 and 2 and 3
5 reno?protect*.ti,ab.
6 4 or 5
7 (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.
8 6 and 7

Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Acute Kidney Injury explode all trees
#2 MeSH descriptor Kidney Failure, Chronic explode all trees
#3 MeSH descriptor Kidney Function Tests explode all trees
#4 MeSH descriptor Glomerular Filtration Rate explode all trees
#5 MeSH descriptor Renal Circulation explode all trees
#6 MeSH descriptor Renal Plasma Flow, Effective explode all trees
#7 MeSH descriptor Renal Insufficiency explode all trees
#8 kidney
#9 glomerul* near filtration
#10 renal near (failure or protect* or function*)
#11 kidney function test*
#12 renal function test*
#13 free water clearance
#14 (fractional excretion) of sodium
#15 urine near (output or flow)
#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#18 diuretic* or mannitol or frusemide or furosemide
#19 MeSH descriptor Fluid Therapy explode all trees
#20 fluid* near therap*
#21 MeSH descriptor Infusions, Intravenous explode all trees
#22 (intravenous near fluid*) or hydration
#23 angiotensin converting enzyme inhibitor*
#24 ACE inhibitor*
#25 MeSH descriptor Diuretics explode all trees
#26 MeSH descriptor Mannitol explode all trees
#27 MeSH descriptor Furosemide explode all trees
#28 MeSH descriptor Dopamine explode all trees
#29 MeSH descriptor Dopamine Agonists explode all trees
#30 dopamin*
#31 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
#32 MeSH descriptor Perioperative Care explode all trees
#33 MeSH descriptor Intraoperative Care explode all trees
#34 MeSH descriptor Intraoperative Complications explode all trees
#35 MeSH descriptor Intraoperative Period explode all trees
#36 perioperativ* or intraoperativ*
#37 (#32 OR #33 OR #34 OR #35 OR #36)
#38 (#16 AND #31 AND #37)

Appendix 2. data extraction form

Data extraction form

Study ID:

Language: English/

What was the surgical procedure?

What was the study intervention?

How many participants were studied?

How many in the intervention group?

How many in the control group?

Were the inclusion criteria clearly defined?

Were the exclusion criteria clearly defined?

Age group	Intervention	Control
-----------	--------------	---------

Male:Female numbers:

Bias:

Was there randomization of allocation in the groups?

Was there adequate information about randomization?

Was there allocation concealment?

Was the allocation concealment adequate?

Were there any withdrawals from the study?

How many people withdrew from each group?

Was there blinding in the study?

Study details:

What was the actual nature of the intervention?

When did the intervention start and finish?

What was the actual nature of the control group?

When did the control group start and finish?

Were the two groups treated equally?

What were the outcomes studied?

Mortality

Acute renal failure

Urine output

Creatinine clearance

Free water clearance

Fractional excretion of sodium

Renal blood flow

Urinary microalbumin:creatinine ratio

Urinary NAG:creatinine ratio

Urinary RBOP:creatinine ratio

Urinary NGAL:creatinine ratio

Plasma cystatin C

When were the outcomes measured?

Preoperative Postoperative: 24 hours Postoperative: 48 hours Postoperative: 72 hours Postoperative: day (note)

Was the outcome assessment blinded?

Was there intention-to-treat analysis?

Are mean and standard deviation given?

Other measures of presentation of data

Graphic data?

Results:

Mean and SD Other measures: (please specify clearly)

Remarks:

Drug company sponsorship?

Other comments:

WHAT'S NEW

Date	Event	Description
9 September 2013	New citation required but conclusions have not changed	<p>We updated the search until August 2012; some of the authors have been changed from the previous version of this review (Zacharias 2008)</p> <p>We included 19 new studies</p> <p>We identified new interventions and incorporated them into the review (N-acetyl cysteine; atrial natriuretic peptide; erythropoietin (EPO))</p> <p>We identified new outcomes in the form of biomarkers of renal damage and added them to the review in keeping with current trends in the literature</p> <p>The conclusions of the new update have not changed from those provided in the previous published version of this review (Zacharias 2008)</p>
9 September 2013	New search has been performed	Major update completed

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2005

Date	Event	Description
7 August 2008	New search has been performed	<p>The following changes from the previous published review are made in this updated review.</p> <p>1. We have modified the search strategy and updated it until June 2007.</p>

Date	Event	Description
		<p>2. A change in members of the review team from the first published review to the present update. Some of the original review authors were no longer available, and other authors have joined the review team.</p> <p>3. Modified search strategy in June 2007 identified further studies, which are incorporated in the updated review.</p> <p>4. Some of the previous studies included in the review have been dropped following further detailed evaluation of the studies and new ones were added.</p> <p>5. There are minor changes in the results following the above modifications, but the conclusions remain the same.</p>
7 August 2008	New citation required but conclusions have not changed	New review team; review has undergone substantial work

CONTRIBUTIONS OF AUTHORS

Dr Mathew Zacharias

Contact reviewer. Involved in development of the protocol, the search strategy, retrieval of the papers, screening of the papers, data extraction and data input and writing of the protocol and review, including the updated review

Dr Mohan Mugawar

Screening of the papers, extraction of data, checking of data input and writing of the updated review

Prof G Peter Herbison

Statistical and general advice, checking of the review

Dr Palvannan Sivalingam

Co-reviewer. Involved with development of the protocol and screening of the papers, data extraction, checking of data input and checking of the review, including the update

Prof Robert J Walker

Specialist advice on kidney and renal function tests

Dr Karen Hovhannisyan

Development of new search strategy and performing the search

Dr Niamh P Conlon

Co-reviewer for the previous version of the review; special advisor on the review

DECLARATIONS OF INTEREST

Mathew Zacharias: none known

Mohan Mugawar: none known

G Peter Herbison: none known

Robert J Walker: none known

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Palvannan Sivalingam: none known

Niamh P Conlon: none known

SOURCES OF SUPPORT

Internal sources

- Dunedin Hospital & Dunedin School of Medicine, Dunedin, New Zealand.

External sources

- None, New Zealand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have included new interventions in this review (*N*-acetyl cysteine, atrial natriuretic peptide, sodium bicarbonate, antioxidants and erythropoietin). We have looked at some of the newer biomarkers of kidney damage (urinary NAG/creatinine ratio; urinary RBP/creatinine ratio; plasma cystatin C; urinary NGAL/creatinine ratio) as surrogate markers for renal damage.

NOTES

This review was published first in 2005 and was updated in 2008 ([Zacharias 2005](#); [Zacharias 2008](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Creatinine [urine]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Renal Insufficiency [*prevention & control]; Surgical Procedures, Operative [*adverse effects]; Urine

MeSH check words

Adult; Humans