ClinicalEvidence

Acute renal failure

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ABSTRACT

INTRODUCTION: Acute renal failure is characterised by abrupt and sustained decline in glomerular filtration rate, which leads to accumulation of urea and other chemicals in the blood. The term acute kidney injury has been recently introduced to encompass a wide spectrum of acute alterations in kidney function from very mild to severe. Acute renal failure/acute kidney injury is classified according to the RIFLE criteria where a change from baseline serum creatinine or urine output determines the level of renal dysfunction. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent acute renal failure in people at high risk? What are the effects of treatments for critically ill people with acute renal failure? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 77 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: albumin supplementation plus loop diuretics (intravenous), aminoglycosides, aminophylline, amphotericin B, calcium channel blockers, contrast media, dialysis membranes, dopamine, fenoldopam, loop diuretics, mannitol, N-acetylcysteine, natriuretic peptides, renal replacement therapy, sodium bicarbonate-based fluids, sodium chloride-based fluids, and theophylline.

QUESTIONS

What are the effects of interventions to prevent acute renal failure in people at high risk? 4

What are the effects of treatments for critically ill people with acute renal failure? 17

INTERVENTIONS

PREVENTION IN HIGH-RISK PEOPLE

Beneficial

Contrast media (low-osmolality more effective than high-osmolality contrast media) 4

Likely to be beneficial

Aminoglycosides (single dose as effective as multiple doses for treating infection, but with reduced nephrotoxicity) 9

Amphotericin B (lipid formulations may cause less nephrotoxicity than standard formulations)* 6

Contrast media (iso-osmolar may be more effective than low-osmolality contrast media) 8

N-Acetylcysteine 6

Sodium chloride based fluids 4

Unknown effectiveness

Renal replacement therapy (prophylactic haemofiltration/dialysis) 12

Sodium bicarbonate-based fluids (limited evidence better than sodium chloride for the prevention of contrast nephropathy) 9

Unlikely to be beneficial

Fenoldopam 10

Mannitol 11

Natriuretic peptides 16

Theophylline or aminophylline 13

Likely to be ineffective or harmful

Calcium channel blockers (for early allograft dysfunction) 14

Dopamine 15

Loop diuretics 16

TREATMENT IN CRITICALLY ILL PEOPLE

Likely to be beneficial

Renal replacement therapy (reduced mortality compared with low-dose) 17

Unknown effectiveness

Albumin supplementation plus loop diuretics (intravenous) 19

Dialysis membranes (unclear if synthetic or cellulose-based membranes more effective) 19

Loop diuretics (unclear if continuous infusion more effective than bolus injection) 18

Renal replacement therapy (unclear whether continuous or intermittent renal replacement therapy more effective) 18

Unlikely to be beneficial

Loop diuretics 20

Likely to be ineffective or harmful

Dopamine 21

Natriuretic peptides 21

To be covered in future updates

Early versus late renal replacement therapy

Extended daily dialysis (versus intermittent haemodialysis [IHD] or continuous renal replacement therapy [CRRT])

Xanthines other than theophylline or aminophylline

Footnote

*Categorisation based on consensus.

Key points

- Acute renal failure is characterised by abrupt and sustained decline in GFR, which leads to accumulation of urea and other chemicals in the blood.

  It can be classified according to a change from baseline serum creatinine or urine output, with "Risk" being defined by either a 50% increase in serum creatinine, or a urine output of less than 0.5 mL/kg/hour for at least 6 hours; and "Failure" being defined by a threefold increase in serum creatinine, or a urine output of less than 0.3 mL/kg/hour for 24 hours.

- In people at high risk of developing acute renal failure, intravenous sodium chloride (0.9%) reduces incidences of acute renal failure compared with unrestricted oral fluids or 0.45% iv sodium chloride solution.

  N-acetylcysteine plus intravenous fluids may reduce contrast nephropathy compared with intravenous fluids alone in people undergoing contrast nephrography, although data about prevention of renal failure are inconclusive.

  Low-osmolality contrast medium is less nephrotoxic compared with high-osmolality media, and iso-osmolar contrast media may be less nephrotoxic compared with low-osmolar contrast media.

  We found insufficient evidence on the effects of prophylactic renal replacement therapy.

  Single-dose aminoglycosides seem as beneficial as multiple doses for treating infections, but are less nephrotoxic.

  Lipid formulations of amphotericin B may cause less nephrotoxicity than standard formulations, although the evidence for this is somewhat sparse.

  Mannitol, theophylline, aminophylline, fenoldopam, and calcium channel blockers do not seem useful treatments for people at high risk of acute renal failure.

- In critically ill people, high-dose continuous renal replacement therapy may reduce mortality compared with low-dose, although we don't know whether continuous therapy is any more effective than intermittent renal replacement therapy.

  Synthetic dialysis membranes may be associated with improved survival compared with cellulose-based membranes for treating people with acute renal failure; however, evidence is inconclusive and of variable quality.

  Loop diuretics plus fluids seems to increase the risk of developing acute renal failure compared with fluids alone, both in high-risk and critically ill people, and do not seem to improve renal function or mortality compared with placebo in people with acute renal failure, but may increase the risks of ototoxicity and volume depletion.

  We found no evidence that examined whether intravenous albumin supplementation improved the effects of loop diuretics, or whether continuous infusion was any more effective than bolus injection in the treatment of people critically ill with acute renal failure.

- Neither natriuretic peptides nor dopamine seem beneficial in either high-risk or critically ill people, and both are associated with significant side effects.

DEFINITION

Acute renal failure is characterised by abrupt and sustained decline in glomerular filtration rate (GFR), [1] which leads to accumulation of urea and other chemicals in the blood. Most studies define it biochemically as a serum creatinine of 2–3 mg/dL (200–250 µmol/L), an elevation of more than 0.5 mg/dL (45 µmol/L) over a baseline creatinine below 2 mg/dL, or a twofold increase of baseline creatinine. A recent international interdisciplinary consensus panel has classified acute renal failure (now termed acute kidney injury) according to a change from baseline serum creatinine or urine output. The three-level classification begins with "Risk" (defined by either a 50% increase in serum creatinine or a urine output of less than 0.5 mL/kg/hour for at least 6 hours), and concludes with "Failure" (defined by a threefold increase in serum creatinine or a urine output of less than 0.3 mL/kg/hour for 24 hours). [2] Acute renal failure is usually additionally classified according to the location of the predominant primary pathology (prerenal, intrarenal, and postrenal failure). Critically ill people are clinically unstable and at imminent risk of death, which usually implies that they need to be in, or have been admitted to, the intensive care unit (ICU).

INCIDENCE/ PREVALENCE

Two prospective observational studies (2576 people) found that established acute renal failure affected nearly 5% of people in hospital, and as many as 15% of critically ill people, depending on the definitions used. [3] [4]

AETIOLOGY/ RISK FACTORS

General risk factors: Risk factors for acute renal failure that are consistent across multiple causes include: age; hypovolaemia; hypotension; sepsis; pre-existing renal, hepatic, or cardiac dysfunction; diabetes mellitus; and exposure to nephrotoxins (e.g. aminoglycosides, amphotericin, immunosuppressive agents, NSAIDs, ACE inhibitors, intravenous contrast media) (see table 1, p 26). [4] [5] [6] [7] [8] **Risk factors/aetiology in critically ill people:** Isolated episodes of acute renal failure are rarely seen in critically ill people, but are usually part of multiple organ dysfunction syndromes. Acute renal failure requiring dialysis is rarely seen in isolation (less than 5% of people). The kidneys

are often the first organs to fail. [9] In the perioperative setting, risk factors for acute renal failure include prolonged aortic clamping, emergency rather than elective surgery, and use of higher volumes (greater than 100 mL) of intravenous contrast media. One study (3695 people) using multiple logistic regression identified the following independent risk factors: baseline creatinine clearance below 47 mL/minute (OR 1.20, 95% CI 1.12 to 1.30), diabetes (OR 5.5, 95% CI 1.4 to 21.0), and a marginal effect for doses of contrast media above 100 mL (OR 1.01, 95% CI 1.00 to 1.01). Mortality of people with acute renal failure requiring dialysis was 36% while in hospital. [5] Prerenal acute renal failure is caused by reduced blood flow to the kidney from renal artery disease, systemic hypotension, or maldistribution of blood flow. Intrarenal acute renal failure is caused by parenchymal injury (acute tubular necrosis, interstitial nephritis, embolic disease, glomerulonephritis, vasculitis, or small-vessel disease). Postrenal acute renal failure is caused by urinary tract obstruction. Observational studies (in several hundred people from Europe, North America, and West Africa with acute renal failure) found a prerenal cause in 40–80%, an intrarenal cause in 10–50%, and a postrenal cause in the remaining 10%. [7] [8] [10] [11] [12] [13] Prerenal acute renal failure is the most common type of acute renal failure in critically ill people. [7] [14] Intrarenal acute renal failure in this context is usually part of multisystem failure, most frequently due to acute tubular necrosis due to ischaemic or nephrotoxic injury, or both. [15] [16]

PROGNOSIS

One retrospective study (1347 people with acute renal failure) found that mortality was less than 15% in people with isolated acute renal failure. [17] One recent prospective study (more than 700 people) found that, in people with acute renal failure, overall mortality (72% in ICU *v* 32% in non-ICU; P = 0.001) and the need for dialysis (71% in ICU *v* 18% in non-ICU; P less than 0.001) were higher in an ICU than in a non-ICU setting, despite no significant difference between the groups in mean maximal serum creatinine (5.21 ± 2.34 mg/dL in ICU *v* 5.82 ± 3.26 mg/dL in non-ICU). [18] One large study (more than 17,000 people admitted to Austrian ICUs) found that acute renal failure was associated with a higher than fourfold increase in mortality. [19] Even after controlling for underlying severity of illness, mortality was still significantly higher in people with acute renal failure (62.8% in people with acute renal failure *v* 38.5% in people with no acute renal failure), suggesting that acute renal failure is independently responsible for increased mortality, even if dialysis is used. However, the exact mechanism that leads to increased risk of death is uncertain. A systematic review including 80 articles and a total of 15,897 people with acute renal failure from 1970–2004 found mortality unchanged at about 50%, and exceeding 30% in most studies. [20] An observational study including 54 sites and 23 countries screened 29,269 people, and found that 1738 (5.7%) had severe acute renal failure warranting renal replacement therapy. Overall hospital mortality among people with severe acute renal failure was 60.3% (95% CI, 58.0% to 62.6%). [21]

AIMS OF INTERVENTION

Prevention: To preserve renal function. **Treating critically ill people:** To prevent death; to prevent complications of acute renal failure (volume overload, acid–base disturbance, and electrolyte abnormalities); and to prevent the need for chronic dialysis, with minimum adverse effects.

OUTCOMES

Prevention: Rates of acute renal failure, nephrotoxicity, or both. Surrogate outcomes were limited to measurements of biochemical evidence of organ function (serum creatinine or creatinine clearance) after the intervention. Surrogate markers such as urine output or renal blood flow were not considered as evidence of effectiveness. **Critically ill people:** Rate of death; rate of renal recovery; adverse effects of treatment.

METHODS

BMJ Clinical Evidence search and appraisal April 2007. The following databases were used to identify studies for this review: Medline 1966 to April 2007, Embase 1980 to April 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 people, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies for the question on treating acute renal failure; there needed to be at least a 48-hour follow-up for the question pertaining to prevention. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 27).

QUESTION What are the effects of interventions to prevent acute renal failure in people at high risk?

OPTION CONTRAST MEDIA (LOW-OSMOLALITY)

Kidney injury

Low-osmolality contrast media compared with high-osmolality contrast media Low-osmolality contrast media are more effective at reducing nephrotoxicity, particularly in people with underlying renal failure, but are no more effective at reducing the development of acute renal failure or the need for dialysis (moderate-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Low-osmolality contrast media versus high-osmolality contrast media:
We found one systematic review (search date 1991, 31 RCTs, 5146 people receiving intravascularly administered iodinated contrast material) comparing low-osmolality contrast media with high-osmolality contrast media. [22] The review found no significant difference between low-osmolality and high-osmolality contrast media in the development of acute renal failure or need for dialysis (these are rare events), but there was less nephrotoxicity with low-osmolality contrast media, measured by serum creatinine. Subgroup analysis found that low-osmolality contrast media significantly reduced the proportion of people with a rise in serum creatinine of 44 µg/L or more compared with high-osmolality contrast media in people with underlying renal failure. It found no significant difference between treatments for people without prior renal failure (prior underlying renal impairment, 8 RCTs, 1418 people: OR 0.50, 95% CI 0.36 to 0.68; no underlying renal impairment, 20 RCTs, 2865 people: OR 0.75, 95% CI 0.52 to 1.10).

Low-osmolality contrast media versus iso-osmolar contrast media:
See benefits of iso-osmolar contrast media, p 8 .

Harms:

Low-osmolality contrast media versus high-osmolality contrast media:
The review did not report any adverse effects.

Low-osmolality contrast media versus iso-osmolar contrast media:
See harms of iso-osmolar contrast media, p 8 .

Comment: None.

OPTION SODIUM CHLORIDE-BASED FLUIDS

Kidney injury

Intravenous sodium chloride 0.9% compared with oral fluids Intravenous sodium chloride seems more effective at reducing acute renal failure 48 hours after catheterisation in people having elective cardiac catheterisation, but not in people with chronic renal failure undergoing various radiological procedures (moderate-quality evidence).

Sodium chloride 0.9% compared with sodium chloride 0.45% Sodium chloride 0.9% infusion is more effective at reducing contrast nephropathy, particulary in women, in people with diabetes, and in people receiving more than 250 mL of contrast (high-quality evidence).

Sodium chloride 0.45% compared with restricted fluids Preoperative intravenous sodium chloride may be more effective at reducing kidney injury in people with moderate to severe renal insufficiency undergoing cardiac surgery. Hydration may also be more effective at reducing the proportion of people requiring postoperative dialysis (low-quality evidence).

Inpatient compared with outpatient fluid regimens We don't know whether inpatient intravenous fluid regimens are more effective at reducing serum creatinine levels in people with renal dysfunction having cardiac catheterisation (very low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Intravenous sodium chloride 0.9% versus oral fluids:
We found one RCT (53 people having elective cardiac catheterisation with a contrast agent containing iodine), which compared intravenous sodium chloride (sodium chloride 0.9% for 24 hours at a rate of 1 mL/kg/hour begun 12 hours before catheterisation) versus unrestricted oral fluids. [23] It found that sodium chloride hydration significantly reduced acute renal failure compared with unrestricted oral fluids within 48 hours (acute renal failure defined as increase in serum creatinine by at least 44.2 µmol/L [about 0.5 mg/dL]: 1/27 [4%] with sodium chloride intravenous *v* 9/26 [35%] with unrestricted oral fluids; RR 0.11, 95% CI 0.015 to 0.79). A second RCT (312 people with chronic renal failure [serum creatinine 201 ± 81 µmol/L] undergoing various radiological procedures

with a non-ionic, low-osmolality contrast agent) compared four groups: oral sodium chloride 0.1 g/kg of body weight/day for 2 days before the procedure (the oral saline hydration group); intravenous 0.9% sodium chloride 15 ml/kg for 6 hours before the procedure; intravenous 0.9% sodium chloride plus theophylline 5 mg/kg orally 1 hour before the procedure; intravenous 0.9% sodium chloride plus furosemide 3 mg/kg intravenously just after the procedure. [24] Contrast nephropathy was defined as an increase in serum creatinine of 44 µmol/L (0.5 mg/dL), and occurred in 27/312 people (9%) overall. The RCT found no significant difference in contrast nephropathy among groups (5/76 [7%] with oral sodium chloride *v* 4/77 [5%] with intravenous sodium chloride *v* 6/80 [7%] with with oral sodium chloride plus theophylline *v* 12/79 [15%] with intravenous sodium chloride plus furosemide; P greater than 0.05). [24] Older RCTs compared combinations of fluids (especially sodium chloride 0.45% infusion) versus other active treatments. Comparisons between outcomes in these trials and historical untreated controls are difficult to evaluate, but suggest benefit from fluids. [25] In certain settings, such as traumatic rhabdomyolysis, early and aggressive fluid resuscitation has had dramatic benefits compared with historical controls. [6]

Sodium chloride 0.9% versus sodium chloride 0.45%:
We found one RCT (1620 people who had coronary angiography), which compared the effects of sodium chloride 0.9% infusion versus sodium chloride 0.45% in dextrose infusion on contrast nephropathy. [26] Infusion solution was given the morning of the procedure for people having elective surgery, or immediately before surgery in the case of emergency surgery. Contrast nephropathy was defined as an increase in serum creatinine of more than 45 µmol/L (0.5 mg/dL) within 48 hours. The RCT found that sodium chloride 0.9% infusion significantly reduced contrast nephropathy compared with sodium chloride 0.45% in dextrose infusion (0.7% with sodium chloride 0.9% infusion *v* 2.0% with sodium chloride 0.45% infusion; P = 0.04). Three predefined subsets of people (women, people with diabetes, and people receiving more than 250 mL of contrast) benefited the most from sodium chloride 0.9% infusion (reduction in contrast-mediated associated nephropathy; women: reduction from 5.1% to 0.6%; P = 0.01; people with diabetes: reduction from 9.8% to 5.5%; P = 0.01; people receiving more than 250 mL of contrast: reduction from 3.0% to 0%; P = 0.01).

Sodium chloride 0.45% versus restricted fluids:
We found one RCT (45 people with chronic kidney disease undergoing cardiac surgery) which compared intravenous 0.45% sodium chloride prior to surgery versus restricted fluids. [27] People admitted for elective open heart surgery with a quantified GFR of less than 45 mL/min were assigned using a 2:1 randomisation process, to either an intravenous infusion of 0.45% sodium chloride (1 mL/kg/hour) for 12 hours before the operation (hydration group, 30 people) or to fluid restriction (control group, 15 people). It found that kidney injury (defined as at least 25% increase in serum creatinine from baseline) developed in 9/30 (30%) people with hydration compared with 8/15 (53%) people with control (statistical analysis between groups not reported). The RCT found that hydration significantly reduced the proportion of people requiring postoperative dialysis compared with control (0/30 [0%] with hydration v 4/15 [27%] with control; P less than 0.01). [27]

Inpatient versus outpatient fluid regimens:
We found one RCT (36 people with renal dysfunction having cardiac catheterisation), which compared an inpatient intravenous fluid regimen (sodium chloride 0.45% at 75 mL/hour iv for 12 hours before and after cardiac catheterisation) with an outpatient oral fluid regimen (1 L of clear liquids over 10 hours followed by 6 hours of iv fluids starting just before contrast exposure) for the prevention of radiocontrast-induced renal dysfunction. [28] The predefined primary end point was the maximal change in creatinine up to 48 hours after cardiac catheterisation. The RCT found no significant differences between groups in the maximal changes in serum creatinine (0.21 ± 0.38 mg/dL [18 ± 33 µmol/L] for inpatients *v* 0.12 ± 0.23 mg/dL [11 ± 20 µmol/L] for outpatients; P greater than 0.05; no additional data reported). However, this study may have been underpowered to rule out clinically important differences. The outpatient group also received more fluid volume.

Sodium chloride versus sodium bicarbonate:
See benefits of sodium bicarbonate-based fluids, p 12 .

Harms:

The volumes of fluids recommended (e.g. 1 L) and the rates of infusion (generally less than 500 mL/hour) have little potential for harm in most people.

Intravenous sodium chloride 0.9% versus oral fluids:
The RCT (53 people having non-emergency cardiac catheterisation) comparing sodium chloride versus unrestricted oral fluids found no adverse effects with sodium chloride . [23] The second RCT reported one person had vomiting with oral sodium chloride alone, and no other adverse effects in the other three arms. [24]

Sodium chloride 0.9% versus sodium chloride 0.45%:
The RCT found no significant differences in cardiac or peripheral vascular complications between sodium chloride 0.9% and sodium chloride 0.45% plus dextrose (cardiac complications: 5.3% with sodium chloride 0.9% *v* 6.4% with sodium chloride 0.45% plus dextrose; P = 0.59; peripheral vascular complications: 1.6% with sodium chloride 0.9% *v* 1.5% with sodium chloride 0.45% plus dextrose; P = 0.93). [26]

Sodium chloride 0.45% versus restricted fluids:
The RCT did not report on harms. [27]

Inpatient versus outpatient fluid regimens:
The RCT comparing inpatient versus outpatient fluid regimen gave no information on adverse effects. [28]

Sodium chloride versus sodium bicarbonate:
See harms of sodium bicarbonate-based fluids, p 12 .

Comment: **Clinical guide:**
Hypovolaemia is a significant risk factor for acute renal failure. The provision of adequate maintenance fluids is considered important in preventing acute renal failure. Additional fluid loading may be useful because it assures adequate intravascular volume. It also stimulates urine output, theoretically limiting renal exposure time to higher concentrations of nephrotoxins.

OPTION AMPHOTERICIN B (LIPID FORMULATIONS)

We found no direct information about the effects of amphotericin B in people with acute renal failure.

Note
Lipid formulations of amphotericin B seem to cause less nephrotoxicity compared with standard formulations, but direct comparisons of long-term safety are lacking.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review and no RCTs.

Harms: We found no evidence of increased adverse effects from lipid formulations of amphotericin B. However, these formulations are still nephrotoxic and should be used with care.

Comment: A phase II trial of a lipid formulations of amphotericin B (556 people) found an incidence of renal toxicity (defined by any increase in serum creatinine) of 24% (*v* 60–80% with standard formulation of amphotericin B). People with baseline serum creatinine in excess of 2.5 mg/dL (221 µmol/L) on standard amphotericin B showed a significant decrease in serum creatinine when transferred to the lipid formulation (P less than 0.001). [29] One trial found that simply infusing amphotericin B in a lipid solution designed for parenteral nutrition did not result in any benefit, and may be associated with pulmonary adverse effects. [30]

Clinical guide:
Fluid loading can be useful in reducing the risk of acute renal failure from all nephrotoxins. Considerable variability may exist between individual lipid formulations of amphotericin B, in terms of efficacy and safety, hence the current consensus is that lipid formulations of amphotericin B are less nephrotoxic than standard formulations. It is prudent not to use any form of amphotericin B in people with or at high risk of acute renal failure, if an alternated drug treatment is available.

OPTION N-ACETYLCYSTEINE

Kidney injury
Compared with control in the prevention of contrast nephropathy N-acetylcysteine may be more effective at reducing contrast nephropathy (low-quality evidence).

Compared with placebo in the prevention of perioperative acute renal failure N-acetylcysteine is no more effective at reducing the incidence of acute renal failure in people having elective aortic aneurysm surgical repair, or at reducing postoperative acute renal failure in high-risk people having elective or urgent coronary artery bypass grafts (high-quality evidence).

Compared with placebo in the prevention of acute renal failure after hypotension N-acetylcysteine is no more effective at reducing the incidence of acute renal failure in people with new-onset (within 12 hours) hypotension and vasopressor requirement of at least 30 minutes' duration or both (moderate-quality evidence).

Mortality

Compared with control in the prevention of contrast nephropathy N-acetylcysteine is more effective at reducing the rate for a composite end point of death, acute renal failure requiring temporary renal replacement therapy, or the need for mechanical ventilation, in people undergoing primary angioplasty after acute MI (high-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Acetylcysteine versus control in the prevention of contrast nephropathy:
We found seven systematic reviews (search date not reported [31] [32] [33] and 2003 [34] [35] [36] [37]) and two subsequent RCTs. [38] [39] The reviews had slightly different inclusion and exclusion criteria. The number of RCTs included in the reviews ranged from five to 15 RCTs. All the reviews pooled data and found benefit with acetylcysteine compared with control. Many noted significant heterogeneity between included RCTs. The largest systematic review (search date 2003) considered all RCTs that compared changes in renal function between groups receiving and not receiving *N*-acetylcysteine. [37] Trials in which the control group also received active treatment were excluded, although co-intervention directed at both groups was permitted. The review included both published and unpublished RCTs. Contrast nephropathy was typically defined by an increase in serum creatinine of 0.5 mg/dL (45 µmol/L) within 24–48 hours of contrast administration. The review found that *N*-acetylcysteine significantly reduced the incidence of contrast nephropathy compared with control (15 RCTs, 1776 people, RR 0.65, 95% CI 0.43 to 1.00; P = 0.049; see comment below). [37] However, there was evidence of significant heterogeneity across studies (P = 0.02). A further RCT compared standard- versus double-dose *N*-acetylcysteine to prevent contrast nephropathy. [40] In total, 224 people with chronic renal insufficiency (creatinine level at least 1.5 mg/dL [135 µmol/L], creatinine clearance less than 60 mL/minute, or both), scheduled to have coronary, peripheral, or both procedures, were randomly assigned to receive 0.45% saline intravenously and *N*-acetylcysteine at the standard dose (600 mg orally twice daily on the day before and on the day of administration of contrast), or at a double dose (1200 mg orally twice daily on the day before and on the day of administration of contrast) with non-ionic, low-osmolality contrast dye administration. The RCT found that the double dose of *N*-acetylcysteine significantly reduced the proportion of people with an increase of at least 0.5 mg/dL of creatinine concentration 48 hours after the procedure compared with the standard dose (4/114 [4%] with double dose *v* 12/109 [11%] with standard dose; OR 0.29, 95% CI 0.09 to 0.94). [40] The RCT found that people who received a higher volume of contrast media (at least 140 ml) benefited most from the higher dose. In a more recent large, single-centre RCT, 354 people having primary angioplasty after acute MI were randomised to three groups: standard dose *N*-acetylcysteine (600 mg iv bolus before primary angioplasty and 600 mg orally twice daily for the 48 hours after angioplasty; 116 people), double-dose *N*-acetylcysteine (1200 mg iv bolus and 1200 mg orally twice daily for the 48 hours after intervention; 119 people), and placebo (119 people). [41] The incidence of contrast nephropathy (increase in serum creatinine of at least 25% from baseline) was 33% in control group, 15% in the standard *N*-acetylcysteine group, and 8% in the double-dose *N*-acetylcysteine group (P less than 0.001). The rate for the composite end point of death, acute renal failure requiring temporary renal replacement therapy, or the need for mechanical ventilation was 21 (18%) in the control group, eight (7%) in the standard *N*-acetylcysteine group, and six (5%) in the double-dose *N*-acetylcysteine group (P = 0.002). The subsequent RCTs (364 people, [38] 61 people [39] undergoing surgery) found a similar effectiveness with *N*-acetylcysteine for the prevention of contrast nephropathy compared with the systematic reviews.

Acetylcysteine versus placebo in the prevention of perioperative acute renal failure:
One small RCT randomised 42 people having elective aortic aneurysm surgery to oral *N*-acetylcysteine (1200 mg twice daily the day before surgery and 600 mg twice daily after) or placebo. [42] There was no significant difference in the incidence of acute renal failure (defined as an increase in serum creatinine of at least 25% from baseline) between the groups (50% with *N*-acetylcysteine *v* 27% with control; P = 0.16). Another RCT randomised 295 high-risk people having elective or urgent coronary artery bypass graft to intravenous *N*-acetylcysteine (2 intraoperative and 2 postoperative 600 mg doses) or placebo over 24 hours. [43] There was no difference in the proportion of people with postoperative acute renal failure (29.7% with *N*-acetylcysteine *v* 29.0% with placebo; P = 0.89; RR 1.03, 95% CI 0.72 to 1.46).

Acetylcysteine versus placebo in the prevention of acute renal failure after hypotension:
One RCT (142 people) evaluated whether oral *N*-acetylcysteine reduced the incidence of acute renal failure in people with new-onset (within 12 hours) hypotension of at least 30 minutes' duration and vasopressor requirement or both, compared with placebo. [44] People (on medical, cardiac, surgical, trauma/neurosurgical intensive-care units) were randomised to receive either *N*-acetylcysteine or placebo for 7 days in addition to standard supportive therapy. The RCT found no significant difference in the incidence of acute renal failure (defined as at least 0.5 mg/dL increase in creatinine) between groups (11/71 [15%] with *N*-acetylcysteine plus standard care v 12/71 [17%] with placebo plus standard care; P = 0.82). [44]

Harms:

Acetylcysteine versus control in the prevention of contrast nephropathy:
None of the systematic reviews gave any information on adverse effects of *N*-acetylcysteine. [31] [32] [33] [34] [35] [36] [37]

Acetylcysteine versus placebo in the prevention of perioperative acute renal failure:
None of the systematic reviews gave any information on adverse effects of *N*-acetylcysteine. [31] [32] [33] [34] [35] [36] [37] However, *N*-acetylcysteine has been widely used to treat people with paracetamol (acetaminophen) overdose, and has virtually no toxicity at therapeutic levels (see harms of *N*-acetylcysteine in review on paracetamol [acetaminophen] poisoning).

Acetylcysteine versus placebo in the prevention of acute renal failure after hypotension:
The RCT reported that two people taking *N*-acetylcysteine developed rashes (both possibly due to broad-spectrum antibiotics), and three people taking *N*-acetylcysteine had adverse effects attributable to treatment (two people with nausea, one person with intolerance of taste and odour). [44]

Comment:

The primary outcome assessed in the RCTs included in the systematic reviews was radiocontrast-induced nephropathy at 48 hours (defined as an increase in serum creatinine of 0.5 mg/dL [45 µmol/L] or greater than 25% from baseline after 48 hours). [31] [32] [33] [34] [35] [36] [37] The timing and dose of administration of *N*-acetylcysteine differed widely among included RCTs. The largest systematic review so far revealed significant heterogeneity among studies, suggesting differences in patient populations or study methodology not identified by sensitivity analyses. [37] Hence, these results should be interpreted with caution. One cohort study (50 healthy volunteers with normal renal function) found that *N*-acetylcysteine could independently decrease serum creatinine without any effect on GFR. [45] Therefore, the role of *N*-acetylcysteine to prevent acute renal failure remains unclear. The two studies evaluating the role of *N*-acetylcysteine in the prevention of perioperative acute renal failure were limited, in that they were underpowered, or used shorter duration of treatment.

OPTION CONTRAST MEDIA (ISO-OSMOLAR)

Kidney injury
Iso-osmolar contrast media compared with low osmolar contrast media Non-ionic iso-osmolar contrast media seems more effective at reducing contrast media-induced nephropathy in people with diabetes, and in people having coronary angiography with or without a percutaneous coronary intervention (moderate-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

We found two RCTs. [46] [47] The first RCT(129 people with diabetes mellitus treated with insulin or antidiabetic drugs and serum creatinine concentrations of 1.5–3.5 mg/dL [132–308 µmol/L]), compared non-ionic iso-osmolar contrast media (iodixanol) versus low-osmolar (iohexol) contrast media in people having coronary or aortofemoral angiography. [46] It found that iso-osmolar contrast media significantly reduced contrast media-induced nephropathy compared with low-osmolar contrast media (nephropathy, defined as an increase in serum creatinine greater than 0.5 mg/dL [45 µmol/L]: 2/64 [3%] with iso-osmolar contrast media *v* 17/56 [26%] with low-osmolar contrast media; OR 0.09, 95% CI 0.02 to 0.40; see comment below). In the second RCT (300 people with creatinine clearance 60 mL/min or less), iodixanol (a non-ionic iso-osmolar contrast media) or ioxaglate (a low-osmolar contrast media) were used in people having coronary angiography with or without a percutaneous coronary intervention. [47] Contrast nephropathy was defined as an increase in serum creatinine of at least 25% (or at least 0.5 mg/dL [44.2 µmol/L]). The RCT found that the incidence of contrast nephropathy was significantly lower with iodixanol compared with ioxaglate (11/140 [8%] with iodixanol *v* 23/135 [17%] with ioxaglate; OR 0.42, 95% CI 0.19 to 0.89, P = 0.02). In subgroup analysis, it found that the incidence of contrast nephropathy was also significantly lower with iodixanol in people with severe renal impairment, in people with concomitant diabetes, or in people given at least 140 ml of contrast media (severe renal impairment: 31 people, P = 0.02; diabetes: 97 people, P = 0.04; contrast media at least 140 ml: 171 people, P = 0.04). [47]

Harms:

The first RCT found that iso-osmolar contrast media reduced other adverse events compared with low-osmolar contrast media (13/67 [19%] with iso-osmolar contrast media *v* 29/67 [43%] with low-osmolar contrast media; P value not reported). [46] The second RCT found no difference beween groups in a composite safety end point (death, MI, revascularisation, cerebral infarction, dialysis after contrast procedure: 3/140 [2.1%] with iodixanol *v* 3/135 [2.2%] with ioxaglate; statistical analysis between groups not reported). [47]

Comment:

In the first RCT, although both treatment groups received similar volumes of contrast media, neither the volume of contrast media nor the fluid regimens were standardised. [46] One recent analysis of trials comparing different contrast media used a multivariate logistic regression model to show

that risk of contrast nephropathy was similar between low- and iso-osmolar contrast media. [48] It concluded that factors other than osmolality may be important in determining renal toxicity. However, because the study did not pool trial data in a standard meta-analysis fashion, the results can only be considered as hypothesis generating.

OPTION AMINOGLYCOSIDES (SINGLE DOSE)

Kidney injury
Single-dose aminoglycosides compared with multiple doses Single-dose aminoglycosides seem more effective at reducing nephrotoxicity in people with fever, but not in people with fever and neutropenia (low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found one systematic review [49] and one additional RCT. [50] The systematic review (search date 1995, 4 RCTs, 803 people with fever and neutropenia, not limited to people in intensive care units) found no significant difference between single and multiple doses of aminoglycosides in antimicrobial efficacy, clinical cure rates, and nephrotoxicity (antimicrobial efficacy: 2 RCTs, 57 people: RR 1.00, 95% CI 0.86 to 1.16; clinical cure rates: 4 RCTs, 961 episodes: RR 0.97, 95% CI 0.91 to 1.05; nephrotoxicity, defined as increase in serum creatinine by greater than 35–45 µmol/L [about 0.5 mg/dL], 3 RCTs, 718 episodes: RR 0.78, 95% CI 0.31 to 1.94; see comment below). [49] The additional RCT (85 people with fever) compared a once-daily dose of gentamicin versus three-times-daily doses of gentamicin. [50] It found that single dosing significantly reduced nephrotoxicity compared with multiple dosing (defined as an increase in serum creatinine of at least 0.5 mg/dL (45 µmol/L): 2/40 [5%] with single dosing *v* 11/45 [24%] with multiple dosing; RR 0.21, 95% CI 0.05 to 0.87; NNT 5, 95% CI 2 to 24). [50]

Harms: The review found no evidence of greater harm from once-daily aminoglycoside dosing (see RR of nephrotoxicity in benefits section above). [49]

Comment: The systematic review defined clinical cure according to the definitions used by investigators in the primary studies, which may have varied among studies. [49] The risk from aminoglycosides is highest in people with: volume depletion; underlying renal, cardiac, or hepatic disease; or when combined with diuretics or other nephrotoxic agents. Two studies included in the systematic review randomised episodes of infection, allowing for people to be included in more than one option in the study. [22]

OPTION SODIUM BICARBONATE-BASED FLUIDS

Kidney injury
Compared with sodium chloride Sodium bicarbonate administered before and after contrast exposure may be more effective at reducing contrast-induced nephropathy (low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: **Sodium bicarbonate versus sodium chloride:**
We found one single-centre RCT (119 people having contrast examination with stable serum creatinine levels of at least 1.1 mg/dL [97.2 µmol/L]) comparing a 154 mmol/L infusion of either sodium chloride or sodium bicarbonate, both in 5% dextrose solution. [51] People received either sodium chloride or sodium bicarbonate solution as a bolus of 3 mL/kg an hour for 1 hour before iopamidol contrast administration, followed by an infusion of 1 mL/kg an hour for 6 hours after the procedure. Serum creatinine levels were measured at baseline and at 1 and 2 days after contrast administration. Contrast-induced nephropathy was defined as an increase of at least 25% in serum creatinine within 2 days of contrast. The RCT found that sodium bicarbonate significantly reduced contrast-induced nephropathy compared with sodium chloride (1/60 [1.7%] of people with sodium bicarbonate *v* 8/59 [13.6%] of people with sodium chloride; mean difference 11.9%, 95% CI 2.6% to 21.2%). [51] Initially, 137 people had been randomised in the RCT, but 18 (13%, 9 in each group) people did not complete the study and were not included in the analysis.

Harms: **Sodium bicarbonate versus sodium chloride:**
The RCT gave no information on adverse effects.

Comment: The study was limited in that it was underpowered, had significant withdrawal rates in both groups, and did not perform a true intention-to-treat analysis. See comment on sodium chloride-based fluids for clinical guide, p 4 .

OPTION FENOLDOPAM

Kidney injury
Compared with placebo Fenoldopam is no more effective at preventing acute renal failure, or at reducing the need for dialysis in people having invasive cardiovascular procedures, in people with sepsis or in critically ill people with early acute tubular necrosis (high-quality evidence).

Compared with dopamine We don't know whether fenoldopam is more effective at reducing the incidence of acute renal failure (very low-quality evidence).

Compared with other treatments or control We don't know whether fenoldopam is more effective at reducing the risk of acute kidney injury or the need for renal replacement therapy in people in intensive care units, or in people having major surgery (very low-quality evidence).

Mortality
Compared with placebo Fenoldopam is no more effective at reducing mortality in people having invasive cardiovascular procedures, in people with sepsis, or in critically ill people with early acute tubular necrosis (high-quality evidence).

Compared with other treatments or control We don't know whether fenoldopam is more effective at reducing in-hospital death in people in intensive care units, or in people having major surgery (very low-quality evidence).

Note
Fenoldopam may cause hypotension.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Fenoldopam versus placebo:
We found seven RCTs. [52] [53] [54] [55] [56] [57] [58] Four of the RCTs found some improvement in renal perfusion and creatinine clearance, but had weak methods; [52] [53] [54] [55] either they were underpowered, had differences between groups at baseline, did not compare interventions between groups directly, or did not assess valid clinical outcomes. The fifth and largest RCT (double blind, multi-centre, 315 people with creatinine clearance below 60 mL/minute having invasive cardiovascular procedures) compared intravenous fenoldopam mesylate (0.05 µg/kg/minute titrated to 0.10 µg/kg/minute) versus placebo. [56] All people were hydrated, and treatment started 1 hour before angiography and continued for 12 hours. Contrast nephropathy was defined as an increase of 25% or more in serum creatinine level within 96 hours after the procedure. The RCT found no significant difference between fenoldopam and placebo for contrast nephropathy, 30-day mortality, dialysis, or readmission to hospital (contrast nephropathy: 34% with fenoldopam *v* 30% with placebo; RR 1.11, 95% CI 0.79 to 1.57; P = 0.61; 30-day mortality: 2.0% with fenoldopam *v* 3.8% with placebo; P = 0.50; dialysis: 2.6% with fenoldopam *v* 1.9% with placebo; P = 0.72; readmission to hospital: 17.6% with fenoldopam *v* 19.9% with placebo; P = 0.66). [56] In a recent RCT, [57] 300 septic people with baseline serum creatinine concentrations less than 150 µmol/L (about 1.7 mg/dL) were randomised to continuous infusion of either fenoldopam (150 people; 0.09 µg/kg/minute) or placebo (150 people). The primary outcome measure was the incidence of acute renal failure (defined as a serum creatinine concentration increase to greater than 150 µmol/L [approximately below 1.7 mg/dL]) during drug infusion. Although the incidence of acute renal failure was significantly lower in the fenoldopam group compared with the control group (29 people with fenoldopam *v* 51 people with control; P = 0.006), there were no differences between the groups in the incidence of severe acute renal failure or need for dialysis, or in mean survival time (creatinine greater than 300 µmol/L [about 3.3 mg/dL]; 10 with fenoldopam *v* 21 with control; P = 0.056; mean survival time: 47 ± 2 days with fenoldopam *v* 42.1 ± 2.2 days with control; P = 0.068). Another RCT randomised 155 people with early acute tubular necrosis (serum creatinine level increased to 50% greater than admission levels within 24 hours and mean arterial pressure greater than 70 mm Hg) to fenoldopam (80 people; 0.05 µg/kg/minute titrated to 0.2 µg/kg/minute) or placebo (75 people) for 72 hours. [58] There was no significant difference between the groups in the incidence of dialysis or 21-day mortality (dialysis: 16% with fenoldopam *v* 25% with placebo; P = 0.163; 21-day mortality: 14% with fenoldopam *v* 25% with placebo; P = 0.068).

Fenoldopam versus dopamine:
Two RCTs compared fenoldopam versus low-dose dopamine in the prevention of acute renal failure. [59] [60] The first RCT randomised 100 critically ill adults with early renal dysfunction (intensive care unit stay less than 1 week; haemodynamic stability; and urine output 0.5 mL/kg or less over a 6-hour period, or serum creatinine concentration 1.5–3.5 mg/dL [135–315 µmol/L], or both) to dopamine (2 µg/kg/minute) or fenoldopam mesylate (0.1 µg/kg/minute) continuous infusion for 4 days. [59] Systemic haemodynamic and renal function variables were recorded daily. The RCT found no differences between groups in heart rate, or in systolic, diastolic, or mean arterial pressure. Fenoldopam produced a more significant reduction in creatinine concentration compared with

dopamine after 2, 3, and 4 days of infusion (change from baseline; at day 2: –0.32 mg/dL [–29 µmol/L] with fenoldopam *v* –0.03 mg/dL [–3 µmol/L] with dopamine; P = 0.047; at day 3: –0.45 mg/dL [–41 µmol/L] with fenoldopam *v* –0.09 mg/dL [–8 µmol/L] with dopamine; P = 0.047; at day 4: –0.041 mg/dL [–4 µmol/L] with fenoldopam *v* –0.09 mg/dL [–8 µmol/L] with dopamine; P = 0.02). The RCT did not evaluate clinically relevant end points such as need for dialysis, survival, or renal recovery. In the second RCT, 80 high-risk people having cardiac surgery were randomised to either fenoldopam (0.05 µg/kg/minute) or dopamine (2.5 µg/kg/minute) for a 24-hour period after the induction of anaesthesia. [60] The RCT found no significant difference in incidence of acute renal failure between groups (17/40 [42%] with fenoldopam *v* 16/40 [40%] with dopamine; P = 0.9).

Fenoldopam versus other treatments or control:
One systematic review (search date 2005, 16 RCTs, 1290 people) pooled results of RCTs evaluating fenoldopam compared with placebo or other active treatments in people on intensive care units or in people undergoing major surgery. [61] It included RCTs comparing fenoldopam versus a control treatment in people in surgical or intensive care, but excluded RCTs in which people were administered radiocontrast dye. Of the 16 included RCTs, 4 had been reported only as abstracts. Five RCTs were performed in cardiac surgery, 3 RCTs in vascular surgery, 2 RCTs in liver transplanation, 1 RCT in renal transplantation, and 5 RCTs were performed in the intensive care unit. It reported that fenoldopam dosage varied across studies, and that there was no standardisation of indications for renal replacement therapy and biochemical definitions for acute kidney injury. [61] The pooled analysis included RCTs comparing fenoldopam versus placebo (10 RCTs), versus dopamine (4 RCTs), versus dopamine or dobutamine after loop diuretics (1 RCT) or versus a control which was not reported (1 RCT). Many included RCTs had weak methods. It did not report a seperate analysis of fenoldopam versus placebo alone or versus dopamine alone. The review found that, compared with the combined control, fenoldopam significantly reduced the risk for acute kidney injury, the need for renal replacement therapy, and in-hospital death (acute kidney injury: 11 RCTs, 1094 people, OR 0.43, 95% CI 0.32 to 0.59; P less than 0.001; need for renal replacement therapy: 11 RCTs, 1094 people, OR 0.54, 95% CI 0.34 to 0.84; P = 0.007; in-hospital death: 11 RCTs, 1028 people, OR 0.64, 95% CI 0.45 to 0.91; P = 0.01). These benefits were associated with a significantly shorter intensive care stay compared with the combined control (11 RCTs, 840 people, WMD −0.61 days; 95% CI, −0.99 to −0.23 days; P = 0.002). [61] However, the results are difficult to interpret given the heterogenous combined control (including placebo, dopamine, and other unspecified treatment) and diversity between included RCTs. Given the limitations of the studies analysed (most were small, diverse, some had weak methods including inadequate or unclear allocation concealment, high risk of bias, and incomplete reporting of methods, and many were not placebo controlled), the review recommends that a large placebo-controlled trial is needed. [61]

Harms:

Fenoldopam versus placebo:
Only two of the five RCTs reported data on potential adverse effects of fenoldopam. [54] [56] One RCT (45 people) found that fenoldopam significantly lowered the mean arterial pressure within 30 minutes of the infusion, and for the entire 4-hour infusion after angiography compared with sodium chloride. [54] The largest RCT found that fenoldopam significantly decreased blood pressure (P = 0.001), and increased heart rate (P = 0.01) compared with placebo (results presented graphically). [56] It found that fenoldopam treatment had to be stopped more often than placebo, most commonly for mild hypotension or tachycardia. It found no significant difference for the combined adverse-effects outcome of death, dialysis, MI, or readmission to hospital (23.4% with fenoldopam *v* 23.1% with placebo; P greater than 0.99).

Fenoldopam versus dopamine:
In the RCT comparing fenoldopam with low-dose dopamine, fenoldopam did not cause any clinically significant haemodynamic impairment compared with low-dose dopamine. [59]

Fenoldopam versus other treatments or control:
The systematic review found that fenoldopam was associated with a non-significant trend towards a greater rate of hypotensive episodes or use of vasopressors compared with the combined control (118/498 [24%] people with fenoldopam *v* 103/544 [19%] people with the combined control; OR 1.31, 95% CI 0.93 to 1.83; P = 0.12). [61]

Comment: None.

OPTION MANNITOL

Kidney injury
Mannitol plus intravenous fluids compared with intravenous fluids Mannitol plus intravenous fluids may be no more effective at reducing the incidence of acute renal failure (low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review. Several small RCTs found no reduction in the incidence of acute renal failure with mannitol plus intravenous fluids compared with intravenous fluids alone in a variety of conditions, including: coronary artery bypass surgery; [62] traumatic rhabdomyolysis; [63] and vascular, [64] and biliary tract surgery. [65] One RCT comparing sodium chloride 0.45% alone, furosemide plus sodium chloride 0.45%, and mannitol plus sodium chloride 0.45% (78 people with chronic renal insufficiency who had a cardiac angiography, mean serum creatinine 2.1 ± 0.6 mg/dL [186 ± 53 µmol/L]) found that mannitol plus sodium chloride 0.45% increased acute renal failure (defined as an increase in serum creatinine of at least 0.5 mg/dL [45 µmol/L] at 48 hours) compared with sodium chloride 0.45% alone, although the difference was not significant (AR: 7/25 [28%] with mannitol *v* 3/28 [11%] with sodium chloride 0.45%; RR 2.61, 95% CI 0.76 to 9.03). [25]

Harms: The RCT gave no information on adverse effects. [25]

Comment: Mannitol is an intravascular volume expander and may function as a free radical scavenger as well as an osmotic diuretic. The RCT addressing the effect of mannitol on renal function provided a three-way comparison showing significant differences among the three groups (P less than 0.05). [25] Although the same control group seems to have been used to compare both interventions, no adjustment was made for multiple comparisons.

OPTION RENAL REPLACEMENT THERAPY (PROPHYLACTIC HAEMOFILTRATION/DIALYSIS)

Kidney injury
Compared with isotonic saline Haemofiltration or haemodialysis (pre- and post- regimens) may be more effective at reducing contrast nephropathy and the need for dialysis in people with baseline chronic renal failure (very high risk of developing contrast nephropathy) having diagnostic and therapeutic cardiovascular procedures with contrast (very low-quality evidence).

Mortality
Compared with isotonic saline Haemofiltration or haemodialysis (pre- and post- regimens) may be more effective at reducing mortality in people with baseline chronic renal failure (very high risk of developing contrast nephropathy) having diagnostic and therapeutic cardiovascular procedures with contrast (very low-quality evidence).

Note
Haemofiltration is invasive, expensive, and can lead to important clinical complications such as hypotension.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: One single-centre RCT (114 people with baseline chronic renal failure, serum creatinine greater than 2 mg/dL [176.8 µmol/L] having coronary interventions with radiocontrast) compared haemofiltration (58 people, mean ± standard deviation serum creatinine concentration of 3.0 ± 1.0 mg/dL [265.2 ± 88.4 µmol/L]) or isotonic saline (rate of 1 mL/kg of body weight/hour; 56 people, mean serum creatinine concentration 3.1 ± 1.0 mg/dL [274.0 ± 88.4 µmol/L]). [66] Haemofiltration (fluid replacement rate 1000 ml/hour without weight loss) and saline were initiated 4–8 hours before coronary intervention and were continued for 18–24 hours after the procedure was completed. The RCT found that, compared with isotonic saline, haemofiltration significantly improved outcomes including lower rates of contrast nephropathy, temporary requirement for renal replacement therapy, in-hospital mortality, and cumulative 1-year mortality (contrast nephropathy [defined as a 25% increase in serum creatinine]: 5% with haemofiltration *v* 50% with isotonic saline; P less than 0.001; haemodialysis or haemofiltration: 3% with haemofiltration *v* 25% with isotonic saline; P less than 0.001; in-hospital mortality: 2% with haemofiltration *v* 14% with isotonic saline; P = 0.02; cumulative 1-year mortality: 10% with haemofiltration *v* 30% with isotonic saline; P = 0.01; see comment below). A second RCT from the same investigators (92 people with chronic kidney disease [creatinine clearance 30 mL/min or less] having invasive diagnostic and therapeutic cardiovascular procedures with contrast agent) compared three different prophylactic treatments: intravenous 0.9% sodium chloride for 12 hours before and for 12 hours after contrast exposure (control group, 30 people); sodium chloride followed by haemofiltration for 18–24 hours after contrast exposure (post-haemofiltration group, 31 people); and haemofiltration for 6 hours before and for 18–24 hours after contrast exposure (pre-/post-haemofiltration group, 31 people). [67] A non-ionic low-osmolality contrast agent was used. Contrast-induced nephropathy was defined as a greater than 25% increase in creatinine from baseline. The RCT found a significant difference among groups in the proportion of people with contrast-induced nephropathy and people requiring haemodialysis, with lower levels in the haemofiltration groups compared with control (contrast nephropathy: 1/31 [3%] in pre-/post-haemofiltration group *v* 8/31 [26%] in post-haemofiltration group *v* 12/30 [40%] in control group, between-group analysis P = 0.0013; haemodialysis: 0/31 [0%] in pre-/post-haemofiltration group *v* 3/31 [10%] in post-haemofiltration group *v* 9/30 [30%] in control group, between-group analysis, P = 0.002). [67] The RCT reported that nine people died during the hospitalisation period (0/31 [0%] in pre-/post-haemofiltration group *v* 3/31 [10%] in post-haemofiltration

group *v* 6/30 [20%] in control group, between-group analysis, P = 0.03). It reported that all deaths were attributable to cardiovascular causes (3 people with cardiogenic shock, 3 people with multiorgan failure, 2 people with heart failure, 1 person with cardioembolic stroke). Both of these studies are small, single-centre RCTs with several important limitations. [66] [67] Firstly, people received large amounts of radiocontrast (250 mL). Secondly, they did not receive iso-osmotic contrast. In the first RCT, both groups received furosemide, and the control group was treated on the ward (a stepdown unit), whereas the treatment group was cared for in the intensive care unit, with a higher intensity of monitoring. [66] There was a very high incidence of contrast nephropathy (50%) and temporary dialysis requirement (25%) in the control group. The second study had less statistical power (92 people divided into 3 groups) and had similar high rates of contrast nephropathy (40%) and dialysis (30%) in the control group (see comment below). [67]

Harms: The first RCT reported no instances of treatment-associated hypotension in the haemofiltration group, and other complications in this group were minimal. [66] Three people in this group had bleeding at the site of vascular access; in one case, blood transfusion was required. The second RCT did not report any further harms. [67]

Comment: Haemofiltration is expensive, invasive, and can lead to important clinical complications, such as hypotension. Notably, studies of prophylactic haemodialysis to remove contrast dye have shown that, although these techniques can remove the contrast from the circulation, there is no reduction in the risk of contrast nephropathy. [68] One study considered cost-effectiveness of haemofiltration to prevent contrast nephropathy in an economic evaluation using decision analysis. [69] Prophylactic haemofiltration was compared with intravenous saline in people at risk for developing contrast nephropathy having angiography in a tertiary- or quaternary-care hospital. It found that prophylactic haemofiltration could be potentially cost-effective only in a small fraction of people (those with baseline serum creatinine greater than 265 µmol/L [about 2.9 mg/dL]), and remains materially less attractive than other strategies. [69]

OPTION THEOPHYLLINE OR AMINOPHYLLINE

Kidney injury

Compared with control in radiocontrast-induced nephropathy Theophylline or aminophylline may be no more effective at preventing radiocontrast-induced nephropathy in people with adequate hydration, and may attenuate the degree of increase in serum creatinine after radiocontrast administration (very low-quality evidence).

Compared with sodium chloride 0.9% after CABG Theophylline is no more effective at preventing renal impairment after elective CABG (moderate-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Theophylline or aminophylline versus control in radiocontrast-induced nephropathy:
We found one systematic review (search date 2003) which included seven RCTs in which theophylline or aminophylline were used in hospitalised people receiving radiocontrast media. [70] RCTs were included if they reported serum creatinine or creatinine clearance within 48 hours after radiocontrast exposure. However, in two RCTs, baseline serum creatinine was estimated using normal values for age, sex, and weight. The review pooled results for RCTs using theophylline or aminophylline. It found that theophylline or aminophylline significantly attenuated the increase in serum creatinine after contrast administration compared with control (7 RCTs, 480 people, difference in mean change of serum creatinine: 11.5 µmol/L [0.13 mg/dL], 95% CI 5.3 µmol/L [0.06 mg/dL] to 19.4 µmol/L [0.22 mg/dL]). [70] The clinical effect seen from the pooled data is very small (less than 15% change from baseline), and is of unclear clinical significance. No clinically significant effects were reported. In addition, the heterogeneity of studies was not reported. In many of the RCTs included in the review, the hydration status of people receiving the radiocontrast agent was unclear. In one included RCT (80 people with pre-existent mild to moderate renal insufficiency) the GFR was preserved with hydration alone. [71] It found that serum creatinine concentration and creatinine clearance did not change significantly with additional theophylline or placebo. Two (6%) people in the theophylline group and one (3%) in the placebo group developed acute renal failure, defined as an increase in serum creatinine of at least 0.5 mg/dL (44 µmol/L). [71]

Theophylline versus sodium chloride 0.9% after CABG:
We found one RCT (56 people with normal renal function), which compared theophylline (a bolus of 4 mg/kg and a subsequent continuous infusion of 0.25 mg/kg/hour for up to 96 hours) versus sodium chloride 0.9% for prevention of renal impairment after elective coronary artery bypass surgery. [72] It found no significant difference between theophylline and sodium chloride in rates of renal impairment, but the RCT may have been underpowered to detect clinically important differences (renal impairment, defined as an increase in serum creatinine of at least 0.4 mg/dL (35 µmol/L)

from the baseline at day 5 after surgery: 5/28 [18%] with theophylline *v* 4/28 [14%] with sodium chloride; P greater than 0.05).

Harms:

Theophylline or aminophylline versus control in radiocontrast-induced nephropathy:
Theophylline has a narrow therapeutic index and known adverse effects (see harms of theophyllines in review on COPD). The systematic review reported one included RCT (48 people) which had used a low dose of theophylline and had found no adverse effects in study groups. [70] It reported no other data on adverse effects. [70]

Theophylline versus sodium chloride 0.9% after CABG:
The RCT found no difference between the placebo and theophylline groups in the number of people whose study medication was stopped owing to presumed adverse effects. Heart rate and systolic and diastolic blood pressures were similar between the groups.

Comment: None.

OPTION CALCIUM CHANNEL BLOCKERS

Kidney injury
Compared with placebo in people receiving live or cadaveric kidney transplant The calcium channel blocker isradipine is more effective at improving median serum creatinine levels at 3–12 months, but is no more effective at preventing early allograft dysfunction (moderate-quality evidence).

Compared with no calcium channel blockers in people receiving cadaveric kidney transplant Calcium channel blockers given in the perioperative period may be more effective at reducing post-transplant acute tubular necrosis, but not graft loss (very low-quality evidence).

Mortality
Compared with no calcium channel blockers in people receiving cadaveric kidney transplant Calcium channel blockers given in the perioperative period may be no more effective at reducing mortality (very low-quality evidence).

Note
We found no direct information assessing the effects of calcium channel blockers in preventing other forms of acute renal failure. Calcium channel blockers are associated with hypotension and bradycardia.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits:

Calcium channel blockers versus placebo in people receiving live or cadaveric kidney transplant:
We found one RCT, which compared isradipine versus placebo after living and cadaveric renal transplants. [73] The RCT (210 people) found that isradipine significantly improved median serum creatinine levels at 3 and 12 months compared with placebo (3 months: 185 µmol/L [2.0 mg/dL] with isradipine *v* 220 µmol/L [2.4 mg/dL] with placebo; P = 0.002; 12 months: 141 µmol/L [1.4 mg/dL] with isradipine *v* 158 µmol/L [1.6 mg/dL] with placebo; P = 0.021). However, it found no significant difference in the incidence of early allograft dysfunction (34/98 [35%] with isradipine *v* 44/112 [39%] with placebo; RR 1.13, 95% CI 0.79 to 1.62) or duration (9.1 days with isradipine *v* 9.3 days with placebo; P value not reported).

Calcium channel blockers versus no calcium channel blockers in people receiving cadaveric kidney transplant:
We found one systematic review (search date 2005, 10 RCTs, 575 people), which compared calcium channel blockers versus no calcium channel blocker after cadaveric kidney transplantation. [74] It included heterogeneous RCTs, in which any calcium channel blocker was given by any route before or immediately after transplant, to recipient or donor, or added to the perfusate (see comments below). [74] Duration of follow-up, where stated, ranged from 4 weeks to 4 years. None of the included studies mentioned loses to follow-up. The review found that calcium channel blockers in the peritransplant period significantly decreased acute tubular necrosis (7 RCTs, 349 people: RR 0.57, 95% CI 0.40 to 0.82). However, it found no significant difference between treatments for graft loss, mortality, or requirement for haemodialysis postoperatively (graft loss: 6 RCTs, 347 people: RR 0.93, 95% CI 0.44 to 1.97; mortality: 5 RCTs, 284 people: RR 0.86, 95% CI: 0.16 to 4.66; postoperative haemodialysis: 4 RCTs: quantitative results not reported).

Harms:

Calcium channel blockers versus placebo in people receiving live or cadaveric kidney transplant:
The RCT gave no information on adverse effects. [73]

Calcium channel blockers versus no calcium channel blockers in people receiving cadaveric kidney transplant:
The systematic review found insufficient information to comment on adverse effects. [74] However, as a class, calcium channel blockers are associated with hypotension and bradycardia, as well as several less-serious adverse effects. The incidence and nature of adverse effects varies between individual drugs.

Comment: The systematic review [74] did not include the RCT [73] that looked at the effect of isradipine on renal function after renal transplantation, because it included living donors. This RCT is the largest multi-centre RCT to date. Moreover, the implications of the conclusion of this systematic review are unclear because the studies pooled were heterogeneous. The studies differed in terms of drugs used (diltiazem, nifedipine, and gallopamil), dose, route, timing, recipient (transplant recipient or donor), and immunosuppression used after the transplant.

OPTION DOPAMINE

Kidney injury
Compared with placebo Dopamine (including low doses) is no more effective at preventing the development of acute renal failure, or the need for dialysis, in people with or at risk of acute renal insufficiency, or in critically ill people with signs of sepsis (high-quality evidence).

Mortality
Compared with placebo Dopamine is no more effective at reducing mortality (high-quality evidence).

Note
Dopamine is associated with serious adverse effects, such as extravasation necrosis, gangrene, and conduction abnormalities.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found two systematic reviews [75] [76] and one subsequent large RCT. [77] The first systematic review (search date 1999, 17 RCTs, 854 people) examined the effects of any dose of dopamine. [75] It was adequately powered and found no significant difference between dopamine and placebo in mortality, onset of acute renal failure, or need for dialysis (mortality: 11 RCTs, 508 people; 4.7% with dopamine *v* 5.6% with placebo; RR 0.83, 95% CI 0.39 to 1.77; onset of acute renal failure: 11 RCTs, 511 people; 15.3% with dopamine *v* 19.5% with placebo; RR 0.79, 95% CI 0.54 to 1.13; dialysis: 10 RCTs, 618 people; 13.9% with dopamine *v* 16.5% with placebo; RR 0.89, 95% CI 0.66 to 1.21). The second systematic review (search date 2000, 15 RCTs, 970 adults either with or at risk of acute renal insufficiency; see comments below) assessed the effects of low-dose dopamine. [76] It was also adequately powered and found no significant difference between low-dose dopamine (2–5 µg/kg/minute) and placebo in acute deterioration in renal function (defined as an increase in serum creatinine of greater than 25% from baseline; AR: 31% with low-dose dopamine *v* 33% with placebo; RR 1.01, 95% CI 0.79 to 1.28). The subsequent RCT (328 critically ill people with signs of sepsis) evaluated dopamine in early renal dysfunction. [77] It found no significant difference between dopamine and placebo in the development of acute renal failure, requirement for dialysis, intensive care unit length of stay, hospital length of stay, or mortality (development of acute renal failure: peak serum creatinine concentration during treatment: 2.7 ± 1.6 mg/dL [245 ± 144 µmol/L] with dopamine *v* 2.8 ± 1.6 mg/dL [249 ± 147 µmol/L] with placebo; P = 0.93; requirement for dialysis: 35/161 [22%] with dopamine *v* 40/163 [25%] with placebo; RR 0.89, 95% CI 0.58 to 1.30; intensive care unit stay: 13 ± 14 days with dopamine *v* 14 ± 15 days with placebo; P = 0.67; hospital stay: 29 ± 27 days with dopamine *v* 33 ± 39 days with placebo; P = 0.29; mortality : 69/161 [43%] with dopamine *v* 66/163 [40%] with placebo; RR 1.06, 95% CI 0.8 to 1.33).

Harms: The systematic reviews [75] [76] and the subsequent RCT in people with sepsis [77] gave no information on adverse effects. Dopamine has known adverse effects, including extravasation necrosis, gangrene, tachycardia, headache, and conduction abnormalities.

Comment: Most of the studies examining the effects of dopamine included people with early indications of renal dysfunction. The distinction between the effects of dopamine for prevention and for treatment is, therefore, blurred. We have used the same studies to infer preventive and treatment effects. One RCT (60 people having CABG) compared four interventions: dopamine, diltiazem, dopamine plus diltiazem, and control (not specified). Drug administration (iv infusion rates diltiazem 2 µg/kg/minute and dopamine 2 µg/kg/minute) was initiated 24 hours before surgery and continued for 72 hours after surgery. [78] Creatinine clearance (primary end point) was significantly higher in the diltiazem-plus-dopamine group compared with the dopamine-only, diltiazem-only, and control groups 24 hours after surgery. However, this study was underpowered, and the hydration status of the people was not controlled. The increase in urine output associated with dopamine is often

thought to be caused exclusively by the increase in renal blood flow and, therefore, it may be confused with evidence of benefit. However, dopamine also has a significant diuretic effect. The review comparing low-dose dopamine versus placebo included: people with normal renal function having elective vascular surgery, cardiac surgery, and liver transplantation; people with obstructive jaundice; people with diabetes; people receiving nephrotoxic drugs or having radiocontrast investigations; and people with renal insufficiency having cardiac surgery or receiving radiocontrast agents. [76]

OPTION LOOP DIURETICS

Kidney injury
Compared with fluids alone Adding loop diuretics to fluids is no more effective at reducing the need for renal replacement therapy or dialysis in people at high risk of acute renal failure (moderate-quality evidence).

Mortality
Compared with fluids alone Adding loop diuretics to fluids is no more effective at reducing in-hospital mortality in people at high risk of acute renal failure (moderate-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found two systematic reviews (search date 1997; [79] search date 2006; [80]), which compared fluids alone versus diuretics plus fluids in people at risk of acute renal failure from various causes. The largest review (search date 2006) compared furosemide versus control, and pooled data. [80] However, the overall analysis included studies in which furosemide was used to prevent acute renal failure (3 RCTs, 325 people) and also to treat acute renal failure (6 RCTs, 623 people). In the overall analysis, the review found no significant difference between furosemide and control in in-hospital mortality, the risk for requiring renal replacement therapy or dialysis, the number of dialysis sessions required, or the proportion of people with persistent oliguria (in-hospital mortality: 7 RCTs [2 RCTs in preventing acute renal failure], 776 people, RR 1.11, 95% CI 0.92 to 1.33; requiring renal replacement therapy or dialysis; 7 RCTs [3 RCTs in preventing acute renal failure], 459 people, RR 0.99, 95% CI 0.80 to 1.22; number of dialysis sessions required: 5 RCTs [no RCTs in preventing acute renal failure], 516 people, WMD –0.48 sessions, 95% CI –1.45 to +0.50 sessions; proportion of people with persistent oliguria: urine output less than 500 ml/day: 3 RCTs [no RCTs in preventing acute renal failure], 183 people, RR 0.54, 95% CI 0.18 to 1.61). There was significant heterogeneity in the results for need for renal replacement therapy or dialysis, and for people who remained oliguric. [80] In an analysis restricted to the three RCTs in which furosemide was solely used to prevent acute renal failure (to prevent acute deterioration in renal function) the review found no significant difference between furosemide and placebo in in-hospital mortality or in the requirement for renal replacement therapy or dialysis (in-hospital mortality: 2 RCTs, 10/103 [10%] with furosemide *v* 4/99 [4%] with placebo, RR 2.33, 95% CI 0.75 to 7.25, P = 0.15; requirement for renal replacement therapy or dialysis: 3 RCTs, 3/128 [2%] with furosemide *v* 0/127 [0%] with placebo, RR 4.08, 95% CI 0.46 to 35.96, P = 0.21). The three preventive studies included people who had cardiac surgery, cardiac angiography, and major general or vascular surgery, and the review noted that treatment protocols with furosemide varied between the studies. The methodological quality of the nine included RCTs was variable (Jadad score: RCTs in preventing acute renal failure, scores 2, 4, and 5; RCTs in treating acute renal failure, scores 1, 1, 1, 1, 3, and 5). [80] The other, older review (search date 1997, 7 RCTs) found no evidence of improved survival, of decreased incidence of acute renal failure, or of need for dialysis associated with diuretics. [79]

Harms: One review found an increased risk of temporary deafness and tinnitus in people treated with high doses of furosemide compared with control, which was of borderline significance (4 RCTs [all RCTs in treatment of acute renal failure], 514 people, RR 3.97, 95% CI 1.00 to 15.78; P = 0.05). [80] One RCT included in this review (81 people after cardiac surgery) in the prevention of acute renal failure found that furosemide plus fluids significantly increased acute renal failure compared with sodium chloride 0.9% alone (6/41 [15%] with furosemide *v* 0/40 [0%] with sodium chloride; NNH 6, 95% CI 3 to 34). [81] The other review did not report on adverse effects. [79]

Comment: None.

OPTION NATRIURETIC PEPTIDES

Kidney injury
Compared with placebo Natriuretic peptides may be no more effective at preventing acute renal failure induced by contrast media in people with stable chronic renal failure. Prolonged infusion of human recombinant atrial natriuretic peptide may be more effective at reducing the proportion of people requiring dialysis (before or at day 21), and the

composite outcome of dialysis or death (before or at day 21), in people with post-cardiac surgical heart failure requiring inotropic and vasoactive support (very low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review. We found one RCT (247 people with stable chronic renal failure, with estimated creatinine clearance of up to 65 mL/minute, scheduled for elective radiographic procedure using a radiocontrast agent) comparing three doses of atrial natriuretic peptide (0.01, 0.05, and 0.10 µg/kg/minute) versus placebo for preventing acute renal failure induced by contrast media. [82] It found a similar incidence of acute renal failure between groups (23% with anaritide 0.01 µg/kg/minute *v* 23% with anaritide 0.05 µg/kg/minute *v* 25% with anaritide 0.10 µg/kg/minute *v* 19% with placebo). [82] One small two-centre RCT compared human recombinant atrial natriuretic peptide versus placebo in 59 people with normal preoperative renal function suffering from post-cardiac surgical heart failure requiring significant inotropic and vasoactive support. [83] Participants received a continuous infusion of either human recombinant atrial natriuretic peptide 50 ng/kg/minute or placebo when serum creatinine increased by more than 50% from baseline. This continued until either the person was discharged from the intensive care unit, serum creatinine decreased below the trigger value for trial inclusion, or predefined criteria for dialysis were fulfilled. The RCT found that human recombinant atrial natriuretic peptide significantly reduced the proportion of people requiring dialysis before or at day 21 compared with placebo (6/29 [21%] with human recombinant atrial natriuretic peptide *v* 14/30 [47%] with placebo; HR 0.28, 95% CI 0.10 to 0.73, P = 0.009). [83] It also found that human recombinant atrial natriuretic peptide significantly reduced the proportion of people with the composite end point of dialysis or death before or at day 21 compared with placebo (8/29 [28%] with human recombinant atrial natriuretic peptide *v* 17/30 [57%] with placebo; HR 0.35, 95% CI 0.14 to 0.82, P = 0.017). [83]

Harms: The RCT evaluating low-dose human recombinant atrial natriuretic peptide found no significant difference between human recombinant atrial natriuretic peptide and placebo in the incidence of hypotension (defined as systolic blood pressure below 90 mm Hg) or atrial fibrillation. [83] See also harms of natriuretic peptides in critically ill people, p 21 .

Comment: Natriuretic peptides (atrial natriuretic peptide and urodilatin) have also been evaluated in the treatment of acute renal failure (see benefits of natriuretic peptides in critically ill people, p 21). The small positive RCT that found benefit with human recombinant atrial natriuretic peptide infusion in postoperative cardiothoracic surgery differed from the previous larger, negative RCTs. [83] The dose used was much smaller (50 ng/kg/minute with small RCT *v* 200 ng/kg/minute with larger RCTs) and the duration of treatment was longer. Further, larger RCTs in this specific population at similar doses and duration are needed to better evaluate the potential effectiveness of this agent.

QUESTION What are the effects of treatments for critically ill people with acute renal failure?

OPTION RENAL REPLACEMENT THERAPY (HIGH-DOSE CONTINUOUS)

Mortality

High-dose continuous renal replacement therapy (haemofiltration) compared with low-dose continuous therapy High-dose continuous renal replacement seems more effective at reducing mortality (moderate-quality evidence).

Haemofiltration compared with haemofiltration plus dialysis Continuous veno-venous haemofiltration is less effective than continuous veno-venous haemodiafiltration at reducing mortality at 28 days (high-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review, but found three RCTs. [84] [85] [86] The first RCT (425 people with acute renal failure) compared three doses of continuous replacement renal therapy (20, 35, and 45 mL/kg/hour of haemofiltration in post-dilution). [84] Mortality was similar for the two high-dose arms (60/139 [43%] with 35 mL/kg/hour *v* 59/140 [42%] with 45 mL/kg/hour), but was significantly higher in the low-dose arm (86/146 [59%] with 20 mL/kg/hour). Survival time analysis was adjusted for three-way comparison (combined RR 1.38, 95% CI 1.14 to 1.67; NNT 7, 95% CI 4 to 16). The second, three-arm RCT (106 severely ill people with oliguric acute renal failure recruited from 2 different centres) compared early, high-dose haemofiltration (72–96 L/day); early, low-dose haemofiltration (24–36 L/day); or late, low-dose haemofiltration (24–36 L/day). [85] It found no significant difference in survival at 28 days between groups, but the study had low power to detect differences. Haemofiltration was started at a mean of 7 hours after inclusion in the "early" groups and 42 hours after inclusion in the "late" group. No significant differences were found in survival at day 28 (26/35 [74%] with early, high-dose *v* 24/35 [69%] with early, low-dose *v* 27/37 [73%] with late, low-dose; P greater than 0.05 for 2- and 3-way comparisons). The third RCT conducted in

two intensive care units compared continuous veno-venous haemofiltration (CVVH; 1–2.5 L/h replacement fluid) versus continuous veno-venous haemodiafiltration (CVVHDF; 1–2.5 L/h replacement fluid plus 1–1.5 L/h dialysate) in 206 people with acute renal failure. [86] The RCT found that survival rates were significantly higher at 28 days and 90 days with CVVHDF compared with CVVH (28 days: 59% with CVVHDF *v* 39% with CVVH, Kaplan–Meier analysis, P = 0.03; 90 days: 59% with CVVHDF *v* 39% with CVVH, Kaplan–Meier analysis, P = 0.0005). [86]

Harms: We found no evidence that the higher dialysis dose was associated with increased adverse effects (such as haemodynamic instability, intolerance, or bleeding). In a prospective study on daily intermittent haemodialysis, there was no evidence of increased morbidity compared with alternate-day dialysis. [87] In particular, hypotension was less common with daily treatment. Two RCTs gave no information on adverse effects. [84] [85] One RCT found similar complications between groups, such as bleeding and filter clotting. [86]

Comment: There is no standard method to compare dialysis dosage between continuous and intermittent renal replacement therapies, but urea kinetic modelling predicts that the doses used in this study would be impossible to achieve without continuous renal replacement therapy. [88] In addition, the underlying mechanisms for solute removal vary with treatment type (convection with haemofiltration compared with diffusion with haemodialysis). This makes comparisons of elimination of diverse solutes difficult. However, a small prospective study (160 people assigned in alternating order to receive daily or conventional haemodialysis) found that a higher dose of dialysis delivered as daily intermittent haemodialysis compared with alternate-day haemodialysis sessions was associated with improved survival in people with acute renal failure (mortality: 28% with daily dialysis *v* 46% with alternate-day dialysis; P = 0.01). [87] Although this study may have had low power to detect important differences, and did not deliver the prescribed dialysis dose, it does support the concept that a dose–response relationship exists for dialysis in acute renal failure, and suggests that the traditional, end-stage renal disease-based dose recommendation may be too low.

OPTION LOOP DIURETICS (CONTINUOUS INFUSION)

We found no clinically important results about continuous infusion compared with bolus injection of loop diuretics in critically ill people with acute renal failure.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review and no RCTs comparing continuous infusion versus bolus injection of loop diuretics in critically ill people with acute renal failure.

Harms: One small crossover RCT (8 people with acute deterioration of chronic renal failure, mean creatinine clearance 0.28 mL/second [16.8 mL/minute]) found that fewer people experienced myalgia when treated with continuous infusion than with a bolus dose of bumetanide (3/8 [38%] people with bolus dose *v* 0/8 [0%] people with continuous infusion). [89]

Comment: The small crossover trial found that continuous infusion resulted in a net increase in sodium excretion over 24 hours (mean increase in sodium excretion 48 mmol/day, 95% CI 16 mmol/day to 60 mmol/day; P = 0.01). [89]

OPTION RENAL REPLACEMENT THERAPY (CONTINUOUS)

Kidney injury
Continuous compared with intermittent renal haemodialysis Continuous and intermittent renal haemodialysis are equally effective at reducing the need for dialysis in critically ill adults with acute renal failure (moderate-quality evidence).

Mortality
Continuous compared with intermittent renal haemodialysis Continuous and intermittent renal haemodialysis are equally effective at reducing mortality in critically ill adults with acute renal failure (moderate-quality evidence). Continuous veno-venous haemodiafiltration and intermittent haemodialysis are equally effective at reducing mortality at 60 days in critically ill people with acute renal failure as part of multiple organ dysfunction syndrome (moderate-quality evidence).

Note
Recent observational data support the choice that continuous renal replacement therapy as initial therapy is associated with better renal recovery.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found one systematic review (search date 2002, 6 RCTs, 624 critically ill adults with acute renal failure). [90] The systematic review compared continuous with intermittent renal haemodialysis. It found no significant difference between continuous and intermittent renal replacement therapy in mortality, renal death, or dialysis dependence among survivors (mortality: RR 0.96, 95% CI 0.85 to 1.08; renal death: RR 1.02, 95% CI 0.89 to 1.17; dialysis dependence: RR 1.19, 95% CI 0.62 to 2.27). One multi-centre RCT conducted in 21 multidisciplinary intensive care units compared the effect of intermittent hemodialysis versus continuous veno-venous hemodiafiltration on 60-day survival rates (the primary end point) in 360 critically ill patients with acute renal failure as part of multiple organ dysfunction syndrome. [91] The RCT found no significant difference between groups in rates of survival at 60 days (32% with intermittent hemodialysis *v* 33% with continuous renal replacement therapy; mean difference 1.1%, 95% CI –8.8 to +11.1%), or at any other time (day 28: 42% *v* 39%, P = 0.65; 90 days: 27% *v* 28%, P = 0.95). [91] However, intermittent hemodialysis was altered to improve tolerance and metabolic control, and may not represent usual practice (see comment below). [91]

Harms: The systematic review gave no information on adverse effects. [90] Heparin is often used with intermittent and continuous renal replacement therapy, and may have adverse effects (see review on thromboembolism). [92] Hypotension is common with intermittent haemodialysis, whereas haemodynamic stability is better preserved with continuous renal replacement therapy. [93]

Comment: The evidence from the systematic review is insufficient to draw conclusions regarding the preferred mode of renal replacement for critically ill people with acute renal failure. [90] A prospective multicentre survey (587 people in 28 intensive care units) found no significant difference in survival between continuous and intermittent renal replacement therapy. [94] Similarly, one RCT (1846 people with chronic rather than acute renal failure receiving chronic treatment with three times weekly sessions) found no survival benefit from increasing the dose of dialysis or from using a high flux membrane. [95] However, we found one earlier systematic review (search date 1998, 13 studies, including 3 RCTs, 1400 critically ill people with acute renal failure), [96] which performed subgroup analysis, adjusting by baseline severity of illness, and found a survival benefit with continuous renal replacement therapy (mortality: RR 0.48, 95% CI 0.34 to 0.69). A secondary analysis in the review, including all studies and adjusting for study quality, found that continuous modalities significantly reduced mortality (RR 0.72, 95% CI 0.60 to 0.87). [96] In a large international prospective cohort of 1218 people treated with continuous renal replacement therapy or intermittant renal replacement therapy for acute renal failure, unadjusted dialysis-independence at hospital discharge was higher after continuous renal replacement therapy (85.5% with continuous renal replacement therapy v 66.2%, with intermittant renal replacement therapy; P less than 0.0001). [97] Multivariate logistic regression showed that choice of continuous renal replacement therapy was not an independent predictor of survival, but was a predictor of dialysis independence at hospital discharge among survivors (OR 3.33, 95% CI 1.85 to 6.02; P less than 0.0001). [97] In a retrospective cohort study between 1995 and 2004 including 2642 people from 32 intensive care units in Scandinavia, continuous renal replacement therapy was associated with better renal recovery (91.7% with continuous renal replacement therapy *v* 83.5% with intermittant renal replacement therapy, OR 2.19, 95% CI 1.35 to 3.53) but mortality did not differ significantly between the groups. [98]

OPTION ALBUMIN SUPPLEMENTATION PLUS LOOP DIURETICS (INTRAVENOUS)

We found no direct information about the effects of intravenous albumin supplementation plus loop diuretics in critically ill people with acute renal failure.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review and no RCTs evaluating clinical outcomes of intravenous albumin supplementation plus loop diuretics in critically ill people with acute renal failure.

Harms: We found no RCTs.

Comment: One crossover RCT (9 people with nephrotic syndrome) compared three interventions: furosemide alone, furosemide plus albumin, and albumin alone. [99] It found that furosemide was superior to albumin alone, and furosemide plus albumin resulted in the greatest urine and sodium excretion. The clinical significance of this finding is unclear.

OPTION DIALYSIS MEMBRANES (SYNTHETIC)

Mortality

Synthetic membranes compared with cellulose-based membranes We don't know whether synthetic dialysis membranes are more effective at reducing mortality in critically ill people with acute renal failure requiring in-centre haemodialysis (very low-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found two systematic reviews comparing synthetic and cellulose-based dialysis membranes in critically ill people with all-cause acute renal failure. [100] [101] The first systematic review (search date 2000, 7 RCTs and controlled clinical trials, 722 people) found no significant difference between synthetic membranes and cellulose-based membranes in mortality among people with acute renal failure requiring in-centre haemodialysis (RR 0.92, 95% CI 0.76 to 1.13). [100] Subgroup analysis revealed that synthetic membranes fared best against unsubstituted cellulose (RR 0.82, 95% CI 0.62 to 1.08), although the result was still not significant. [102] The second systematic review (search date 2000, 8 prospective trials providing survival data, data on recovery of renal function, or both, 867 people) found that synthetic membranes significantly increased survival rates compared with cellulose-based membranes (OR 1.37, 95% CI 1.02 to 1.83; P = 0.03) and showed a non-significant trend toward improved renal recovery (OR 1.23, 95% CI 0.90 to 1.68; P = 0.18). [101] A sensitivity analysis performed by stratifying studies according to the type of membrane used in the control group found that the mortality reduction observed with synthetic membranes was evident when compared with unsubstituted cellulose, but not when compared with modified cellulose.

Harms: Severe anaphylactoid reactions in people taking ACE inhibitors have been reported occasionally with certain synthetic biocompatible membranes (exact frequency unknown). [102]

Comment: Many of the RCTs included in both systematic reviews had methodological limitations, and all studies were underpowered. Differences in effect on outcomes seem most easily demonstrable when synthetic membranes are compared with unsubstituted cellulose. Whether synthetic membranes are superior to modified cellulose (e.g. cellulose triacetate) remains controversial. However, no study has shown an advantage with any cellulose-based membrane over synthetic membranes, except that cellulose-based membranes are generally less expensive.

OPTION LOOP DIURETICS

Kidney injury
Compared with control Loop diuretics may be no more effective at improving renal recovery or at reducing the requirement for renal replacement therapy (very low-quality evidence).

Mortality
Compared with control Loop diuretics may be no more effective at reducing mortality (very low-quality evidence).

Note
Loop diuretics have been associated with ototoxicity and may lead to volume depletion.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found two systematic reviews. [103] [80] The first systematic review (search date 2006, 5 RCTs, 555 people) compared loop diuretics versus control in people with acute renal failure, and pooled data. [103] It included RCTs in adults with established acute renal failure, and which reported at least one of the following: need for renal replacement therapy; death; or renal recovery. Two of the five RCTs (330 people; 92 people) enrolled critically ill people; but the proportion admitted to an intensive care unit was not specified. The review reported that oliguria was variously defined and was present in 258/443 (58%) people in three RCTs; the remaining three RCTs did not report figures for people with oliguria. The review reported that the overall methodological quality and reporting of the RCTs was poor, with only one RCT reporting adequate allocation concealment, while two RCTs did not report loss to follow-up, and one RCT had significant differences between groups at baseline. [103] The review found no significant difference between loop diuretics (mainly furosemide, one RCT with torasemide) and control in mortality or renal recovery (mortality: 4 RCTs, 129/295 [44%] with loop diuretics *v* 84/240 [35%] with control, OR 1.28, 95% CI 0.89 to1.84, P = 0.18; renal recovery: 2 RCTs, 96/228 [42%] with loop diuretics *v* 94/194 [48%] with control, OR 0.88, 95% CI 0.59 to1.31, P = 0.5). The second systematic review included furosemide used both in prevention and treatment of acute renal failure. [80] See benefits of loop diuretics to prevent acute renal failure in people at high risk, p 16 . However, it reported a sub-group analysis for 6 RCTs used to treat renal failure. Of these 6 RCTs, 5 RCTs were included in the first review, and it also included one additional small RCT (56 people). The review found no significant difference between furosemide and placebo in in-hospital mortality, or in requirement for renal replacement therapy (in-hospital mortality: 5 RCTs, 574 people, RR 1.09, 95% CI 0.90 to 1.31; requirement for renal replacement therapy or dialysis: 4 RCTs, 204 people, RR 0.94, 95% CI 0.71 to 1.26). [80]

Harms: See harms of loop diuretics to prevent acute renal failure in people at high risk, p 16 . The first review noted that reporting of harms was inconsistent, and valid estimates of occurence could not be determined. [103] Ototoxicity can occur with high doses of loop diuretics. No adverse effects were reported in one included RCT. [104] Deafness occurred in two people randomised to furosemide in another RCT included in the second review. [105] In one of these people, hearing loss was permanent. [105] The largest RCT included in the reviews reported no significant differences between groups in adverse effects. [106] Diuretics may reduce renal perfusion and add a prerenal component to the renal failure, but the frequency of this event is uncertain. [107] See harms of loop diuretics to prevent acute renal failure in people at high risk, p 16 .

Comment: None.

OPTION DOPAMINE

Kidney injury
Compared with placebo Dopamine is no more effective at reducing the need for dialysis (moderate-quality evidence).

Mortality
Compared with placebo Dopamine is no more effective at reducing mortality (moderate-quality evidence).

Note
Dopamine has been associated with important adverse effects, including extravasation necrosis, gangrene, and conduction abnormalities.

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found one systematic review [75] and one additional RCT. [77] The systematic review (search date 1999, 58 trials, of which 17 were RCTs, 2149 people) found no significant difference between dopamine and placebo in mortality or need for dialysis (mortality: 11 trials, 508 people: 4.7% with dopamine *v* 5.6% with placebo; RR 0.83, 95% CI 0.39 to 1.77; need for dialysis: 10 trials, 618 people: 13.9% with dopamine *v* 16.5% with placebo; RR 0.89, 95% CI 0.66 to 1.21). [75] The additional RCT (multi-centre, double blind, placebo-controlled, 328 people with early renal dysfunction defined as oliguria or increase in serum creatinine) found no significant difference in mortality at discharge between low-dose dopamine and placebo (69/161 [43%] with dopamine *v* 66/163 [41%] with placebo; RR 1.06, 95% CI 0.82 to 1.37). [77]

Harms: Dopamine has recognised adverse effects, including extravasation necrosis, gangrene, tachycardia, headache, and conduction abnormalities. The systematic review [75] and RCT [77] gave no information on adverse effects.

Comment: Studies evaluating dopamine to prevent renal failure or to ameliorate its progression have found no benefit. Studies evaluating the effectiveness of dopamine for the treatment of acute renal failure have focused on early renal dysfunction, and have often included people with normal renal function who were at risk of acute renal failure. The distinction between the effects of dopamine for prevention and treatment is, therefore, blurred, and we have used the same studies to infer preventive and treatment effects.

OPTION NATRIURETIC PEPTIDES

Kidney injury
Compared with placebo Atrial natriuretic peptide is no more effective at reducing dialysis-free survival in oliguric and non-oliguric people with acute renal failure, and ularitide (urodilatin) seems no more effective at reducing the need for dialysis (moderate-quality evidence).

For GRADE evaluation of interventions for acute renal failure, see table, p 27 .

Benefits: We found no systematic review, but found three RCTs. [108] [109] [110] One RCT (504 people with acute tubular necrosis) found no significant difference in dialysis-free survival with atrial natriuretic peptide compared with placebo in people with acute renal failure (43% with anaritide *v* 47% with placebo; P = 0.35). [108] Preplanned subgroup analysis suggested a possible benefit to people with oliguria, but lower survival rates in non-oliguric people. A second RCT (220 people) in people with oliguric acute renal failure found no improvement in dialysis-free survival with a 24-hour infusion of atrial natriuretic peptide compared with placebo. [109] A third RCT compared ularitide (urodilatin, a natriuretic peptide with fewer systemic haemodynamic effects) in a dose-finding (ularitide 5, 20, 40, or 80 ng/kg/minute), placebo-controlled RCT (176 people). Ularitide did not significantly reduce the requirement for dialysis (people treated with dialysis: 35% with ularitide 5 ng/kg/minute *v* 36%

with ularitide 20 ng/kg/minute *v* 28% with ularitide 40 ng/kg/minute *v* 41% with ularitide 80 ng/kg/minute *v* 36% with placebo; P reported as not significant, CI not reported). [110]

Harms: One RCT found that natriuretic peptide caused significant hypotension compared with placebo (95% with natriuretic peptide *v* 55% with placebo; P less than 0.01). Also, atrial natriuretic peptide may be associated with a worse outcome in people with non-oliguric renal failure (dialysis-free survival in 378 non-oliguric people: 48% with anaritide *v* 59% with placebo; RR 0.79, 95% CI 0.64 to 0.97; P = 0.03). [108] See harms of natriuretic peptides in high-risk people, p 16 .

Comment: We found no evidence of significant improvement of acute renal failure with atrial natriuretic peptide.

GLOSSARY

Continuous renal replacement therapy Any extracorporeal blood purification treatment intended to substitute for impaired renal function over an extended period of time and applied, or aimed at being applied, for 24 hours a day.
Early allograft dysfunction Renal dysfunction that occurs after renal transplantation, and which is usually secondary to ischaemic injury.
Early renal dysfunction An acute derangement in renal function that is still evolving.
Intermittent renal replacement therapy Renal support that is not, nor intended to be, continuous; usually prescribed for a period of 12 hours or less.
Lipid formulations of amphotericin B Complexes of amphotericin B and phospholipids or sterols. This reduces the toxicity of amphotericin B while preserving its antifungal activity.
Multiple organ dysfunction syndrome A syndrome of progressive organ failure, affecting one organ after another and believed to be the result of persistent or recurrent infection or inflammation.
Nephrotoxic agents Any agent that has the potential to produce nephrotoxicity.
Nephrotoxicity Renal parenchymal damage manifested by a decline in glomerular filtration rate, tubular dysfunction, or both.
Oliguria Urine output of less than 5 mL/kg daily.
Biocompatible Artificial materials can induce an inflammatory response. This response can be humoral (including complement) or cellular. Synthetic dialysis membranes seem to produce less of an inflammatory response *in vitro* and are classified as more “biocompatible”. By contrast, cellulose-based membranes seem to be less biocompatible (cause more inflammation). When cellulose-based membranes are rendered semi-synthetic by modifications or substitution of materials like acetate, they may be become more biocompatible. We found no standards by which this comparison can be made.
Cellulose-based Dialysis membranes may be made from cellulose. “Unsubstituted” cellulose has not undergone modification to attempt to improve biocompatibility. Synthetic membranes do not use cellulose.
Contrast nephropathy Intravenous radiocontrast increases serum creatinine in some people, particularly those with underlying kidney disease. Most studies define contrast nephropathy as a small change in serum creatinine (e.g. greater than 25% increase). It is not known whether agents that reduce the risk of contrast nephropathy also reduce the risk of acute renal failure.
Glomerular filtration rate The rate of elaboration of protein-free plasma filtrate (ultrafiltration) across the walls of the glomerular capillaries.
High-osmolality contrast media Contrast media with osmolality greater than 800 mOsm/L. Until recently, it was considered the standard formulation for radiological assays.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Iso-osmolar contrast media Contrast media that are iso-osmolar compared with plasma, and therefore of lower osmolality than “low-osmolality contrast media”.
Low-osmolality contrast media Contrast media with osmolality of 600–800 mOsm/L.
Low-quality evidence 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.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Calcium channel blockers The search date of one already included systematic review updated. [74] No new data added to option. Categorisation of 'calcium channel blockers (for early allograft dysfunction)' unchanged (Likely to be ineffective or harmful).
Contrast media (iso-osmolar) One RCT added comparing a non-ionic iso-osmolar contrast media versus a low-osmolar contrast media in people having coronary angiography with or without a percutaneous coronary intervention, which reports the occurrence of contrast nephropathy . [47] Categorisation of 'contrast media (iso-osmolar maybe more effective than low-osmolality contrast media)' unchanged (Likely to be beneficial).
Fenoldopam One systematic review added, which included a meta-analysis comparing the use of fenoldopam versus other treatments combined in people on intensive care units, or in people undergoing major surgery, but excluding people having radiocontrast investigations. [61] The comparison control group in the analysis was comprised of people receiving placebo, dopamine, dopamine or dobutamine, or not stated. Categorisation of 'fenoldepam' unchanged (Unlikely to be beneficial).

Loop diuretics (under question on treatments for critically ill people with acute renal failure) Two systematic reviews added comparing loop diuretics versus control. [103] [80] Benefits and harms data enhanced, categorisation unchanged (Unlikely to be beneficial).

Loop diuretics (under question to prevent acute renal failure in people at high risk) One new systematic review including a pooling of data added comparing furosemide versus control in people at risk of, or with, acute renal failure. [80] Categorisation of 'loop diuretics' unchanged (Likely to be ineffective or harmful).

***N*-Acetylcysteine** Two subsequent RCTs added to the existing reporting of seven systematic reviews comparing *N*-Acetylcysteine versus control in the prevention of contrast nephropathy. [38] [39] One further RCT added comparing *N*-Acetylcysteine versus placebo in the prevention of acute renal failure after hypotension. [44] Categorisation of *N*-Acetylcysteine unchanged (Likely to be beneficial).

Renal replacement therapy (continuous) One multi-centre RCT (360 critically ill people with acute renal failure as part of multiple organ dysfunction syndrome) added to the benefits section comparing the effect of intermittent hemodialysis versus continuous veno-venous hemodiafiltration on 60-day survival rates. [91] Two reports of large cohort studies comparing continuous renal replacement therapy versus intermittant renal replacement therapy for acute renal failure added to the comments section for background information. [97] [98] Categorisation of 'renal replacement therapy (unclear whether continuous or intermittent renal replacement therapy more effective)' unchanged (Unknown effectiveness).

Renal replacement therapy (high-dose continuous) One RCT (206 people) comparing continuous veno-venous haemofiltration (CVVH) versus continuous veno-venous haemodiafiltration (CVVHDF) added. [86] Categorisation of 'renal replacement therapy (reduced mortality compared with low-dose)' unchanged (Likely to be beneficial).

Sodium chloride-based fluids Two RCTs added. [24] [27] The first RCT (312 people) compared intravenous sodum chloride 0.9% versus oral sodium chloride in people with chronic renal failure undergoing various radiological procedures, [24] while the second RCT (45 people) compared intravenous sodium chloride 0.45% versus fluid restriction in people with chronic kidney disease undergoing cardiac surgery. [27] Categorisation of 'sodium chloride-based fluids' unchanged (Likely to be beneficial).

Renal replacement therapy (prophylactic haemofiltration/dialysis) One single-centre RCT (92 people) added comparing pre- and post-haemofiltration, post-haemofiltration, and sodium chloride, in people with baseline chronic renal dysfunction having coronary interventions with contrast. [67] Benefits and harms data enhanced, categorisation of 'renal replacement therapy (prophylactic haemofiltration/dialysis)' changed from Unlikely to be beneficial to Unknown effectiveness.

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Disclaimer

TABLE 1 **Selected risk factors for acute renal failure (see text).**

Risk factor	Incidence of ARF	Comments
Sepsis	Unknown	Sepsis seems to be a contributing factor in as many as 43% of ARF cases [5]
Aortic clamping	Approaches 100% when longer than 60 minutes [6]	Refers to cross-clamping (no flow) above the renal arteries
Rhabdomyolysis	16.5% [7]	None
Aminoglycosides	8–26% [8]	None
Amphotericin	88% with greater than 5 g total dose [9]	60% overall incidence of nephrotoxicity

TABLE **GRADE evaluation of interventions for acute renal failure**

Important outcomes	Kidney injury, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent acute renal failure in people at high risk?									
31 (5146) [22]	Kidney injury	Low-osmolality contrast media *v* high-osmolality contrast media	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (365) [23] [24]	Kidney injury	Intravenous sodium chloride 0.9% *v* oral fluids	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
1 (1620) [26]	Kidney injury	Sodium chloride 0.9% *v* sodium chloride 0.45%	4	0	0	0	0	High	
1 (45) [27]	Kidney injury	Sodium chloride 0.45% *v* restricted fluids	4	−1	0	−1	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (36) [28]	Kidney injury	Inpatient *v* outpatient fluid regimens	4	−2	0	−2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for differences in amount of fluids administered and uncertainty about clinical relevance of outcome measured
17 (2201) [37] [38] [39] [40] [41]	Kidney injury	Acetylcysteine *v* control in the prevention of contrast nephropathy	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs and added for dose response. Directness point deducted for differences in timing and dose administration
1 (354) [41]	Mortality	Acetylcysteine *v* control in the prevention of contrast nephropathy	4	0	+1	−1	0	High	Consistency point added for dose response. Directness point deducted for composite outcome
2 (337) [42] [43]	Kidney injury	Acetylcysteine *v* placebo in the prevention of perioperative acute renal failure	4	0	0	0	0	High	
1 (142) [44]	Kidney injury	Acetylcysteine *v* placebo in the prevention of acute renal failure after hypotension	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
2 (420) [46] [47]	Kidney injury	Iso-osmolar contrast media *v* low osmolar contrast media	4	0	0	−1	0	Moderate	Directness point deducted for not using standardised volumes of contrast media or fluid regimens
4 (803) [49] [50]	Kidney injury	Single-dose aminoglycosides *v* multiple doses	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for people with different disease severities
1 (119) [51]	Kidney injury	Sodium bicarbonate *v* sodium chloride	4	−2	0	0	0	Low	Quality points deducted for sparse data and no intention-to-treat analysis
3 (770) [56] [57] [58]	Kidney injury	Fenoldopam *v* placebo	4	0	0	0	0	High	
3 (770) [56] [57] [58]	Mortality	Fenoldopam *v* placebo	4	0	0	0	0	High	
2 (180) [59] [60]	Kidney injury	Fenoldopam *v* dopamine	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results

Important outcomes	Kidney injury, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
11 (1094) [61]	Kidney injury	Fenoldopam *v* other treatments or control	4	−3	−1	−1	0	Very low	Quality points deducted for incomplete reporting of results and methodological weaknesses. Consistency point deducted for heterogeneity between RCTs. Directness point deducted for heterogenous combined control
1 (78) [25]	Kidney injury	Mannitol plus intravenous fluids *v* intravenous fluids	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for multiple comparisons
2 (206) [66] [67]	Kidney injury	Renal replacement therapy (haemofiltration) *v* isotonic saline	4	−1	0	−2	0	Very low	Quality point deducted for methodological weaknesses. Directness points deducted for differences in treatments provided to both groups and for uncertainty about benefit
1 (114) [66]	Mortality	Renal replacement therapy (haemofiltration) *v* isotonic saline	4	−2	0	−2	0	Very low	Quality points deducted for sparse data and methodological weaknessess. Directness points deducted for differences in treatments provided to both groups
7 (480) [70] [71]	Kidney injury	Theophylline or aminophylline *v* control in radiocontrast-induced nephropathy	4	−2	−1	−1	0	Very low	Quality points deducted for incomplete reporting of results and uncertainty about hydration status of people receiving radiocontrast agent and for uncertainty about heterogeneity between studies. Directness point deducted for uncertainty about clinical significance
1 (56) [72]	Kidney injury	Theophylline *v* sodium chloride 0.9% after CABG	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (210) [73]	Kidney injury	Calcium channel blockers *v* placebo in people receiving live or cadaveric kidney transplant	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (349) [74]	Kidney injury	Calcium channel blockers *v* no calcium channel blockers in people receiving cadaveric kidney transplant	4	−2	−1	0	0	Very Low	Quality points deducted for incomplete reporting of results and for not reporting loss to follow-up or duration. Consistency point deducted for heterogeneity between RCTs
5 (284) [74]	Mortality	Calcium channel blockers *v* no calcium channel blockers in people receiving cadaveric kidney transplant	4	−2	−1	0	0	Very Low	Quality points deducted for incomplete reporting of results and for not reporting loss to follow-up or treatment duration. Consistency point deducted for heterogeneity between RCTs
at least 10 RCTs (at least 618 people) [75] [76] [77]	Kidney injury	Dopamine *v* placebo	4	0	0	0	0	High	
12 (832) [75] [77]	Mortality	Dopamine *v* placebo	4	0	0	0	0	High	
3 (255) [80]	Kidney injury	Loop diuretics *v* fluids alone	4	0	0	−1	0	Moderate	Directness point deducted for differences in treatment protocols
2 (202) [80]	Mortality	Loop diuretics *v* fluids alone	4	0	0	−1	0	Moderate	Directness point deducted for differences in treatment protocols

Important outcomes	Kidney injury, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (3067) [82] [83]	Kidney injury	Natriuretic peptides *v* placebo	4	−1	−1	−2	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness points deducted for composite outcome and for using low doses and long treatment durations
What are the effects of treatments for critically ill people with acute renal failure?									
2 (531) [84] [85]	Mortality	High-dose continuous renal replacement therapy *v* low-dose continuous renal replacement therapy	4	0	0	–1	0	Moderate	Consistency point added for dose response but deducted for conflicting results. Direcntess point deducted for comparing people with different disease severities
1 (206) [86]	Mortality	Haemofiltration *v* haemofiltration plus dialysis	4	0	0	0	0	High	
6 (624) [90]	Kidney injury	Renal replacement therapy (continuous) *v* intermittent renal haemodialysis	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (624) [90]	Mortality	Renal replacement therapy (continuous) *v* intermittent renal haemodialysis	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (360) [91]	Mortality	Renal replacement therapy (intermittent haemodialysis) *v* continuous veno-venous haemodiafiltration	4	0	0	−1	0	Moderate	Directness point deducted for uncertainty about applicability to usual practice
7 + 15 studies (1589) [100] [101]	Mortality	Dialysis membranes (synthetic) *v* cellulose-based	4	−3	−1	0	0	Very low	Quality points deducted for incomplete reporting of results, methodological weaknesses, and for including non-RCTs. Consistency point deducted for conflicting results
at least 2 RCTs (at least 422 people) [103] [80]	Kidney injury	Loop diuretics *v* control	4	−3	0	0	0	Very low	Quality points deducted for poor reporting and methodological weaknesses
5 (at least 574 people) [103] [80]	Mortality	Loop diuretics *v* control	4	−3	0	0	0	Very low	Quality points deducted for poor reporting and methodological weaknesses
10 (618)) [75]	Kidney injury	Dopamine *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of trials
1 RCT + 11 trials (832) [75] [77]	Mortality	Dopamine *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of trials
3 (900) [108] [109] [110]	Kidney injury	Natriuretic peptides *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio