National Institute for Health and Care Excellence

Final

Acute kidney injury: prevention, detection and management

[A] Evidence review for preventing contrast-induced acute kidney injury

NICE guideline NG148

Evidence review underpinning recommendations 1.2.7, 1.2.8 and 1.2.10 and recommendations for research in the NICE guideline

December 2019

Final

This evidence review was developed by NICE

Update information

October 2024: NICE's recommendations on assessing risk factors in adults having iodine-based contrast media were updated in the guideline on acute kidney injury. In addition, the term 'contrast-induced kidney injury' has been changed to 'contrast-associated injury' in recommendation 1.2.7 in line with current terminology.

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Preventing contrast-induced acute kidney injury

Review question

What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?

Introduction

Exposure to iodinated contrast media has been associated with in-hospital AKI. Acute kidney injury following administration of iodinated contrast has previously been referred to as contrast induced nephropathy (CIN). The Kidney Disease: Improving Global Outcomes (KDIGO) international guideline proposes adopting the term contrast induced AKI (CI-AKI) and applying the KDIGO AKI definition. This will provide the opportunity to standardise the terminology used to define AKI and stage its severity. Contrast induced-AKI is uncommon in the general population, with an incidence of 1-2%, and occurs within 72 hours of receiving iodinated contrast media, usually recovering over the following five days. Its incidence increases significantly in patients with risk factors and is associated with prolonged hospital stay, increased mortality and increased health care costs. The risk of CI-AKI has been reported to be as high as 25% in patients with a combination of chronic kidney disease (CKD) and diabetes, cardiac failure, older age and exposure to nephrotoxic drugs.

The NICE guideline on acute kidney injury: prevention, detection and management (NICE guideline CG169) was reviewed in 2017 as part of NICE's surveillance programme in an exceptional review. The purpose of the exceptional review was to examine any impact on the acute kidney injury guideline following the publication of the AMACING study (Nijssen et al 2017), which compared the effectiveness of no prophylaxis to intravenous volume expansion with 0.9% sodium chloride, in people referred for an elective procedure requiring intravascular-iodinated contrast material who were at high risk of CI-AKI. The results showed non-inferiority of either treatment. This new trial result was seen as potentially sufficient to change the existing recommendations. As a result, the decision was made to update this part of the guideline.

The aim of this review is to assess the clinical and cost effectiveness of NAC and/or fluids in preventing CI-AKI in at risk adults. This review identified randomised controlled trials (RCTs) that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

PICO table

Table 1: PICO table for preventing Contrast induced acute kidney injury review

Population	Adults (18 and older) who are at risk (as defined by the study author) of contrast induced AKI.
Intervention	• Sodium chloride 0.9% and 0.45% • Sodium bicarbonate • Oral fluids • N-acetylcysteine (NAC) • Balanced electrolyte solutions (Hartmanns, PlasmaLyte)

	• Other intravenous fluids • Combinations of above interventions Key data to be extracted for each intervention: • Agent • Regime • Duration • Dosage (volume per kg per unit time) Both pre- and post- procedure
Comparator	• Each other • Placebo (for NAC) • No treatment
Outcome	For the pairwise analysis **Primary outcomes** • Contrast induced AKI (as defined by study (usually 48-72 hours, but diagnosed within 7 days of contrast being given to allow for delays in testing) • CKD progression at 3 months after diagnosis of CI-AKI • Mortality (up to 1 year) • Number of patients needing renal replacement therapy (timescale defined by study authors) • Adverse events (including heart failure, as reported by study) Outcomes used for NMA may not include all of these depending on ability to make meaningful connected networks. **Other outcomes of interest:** • Length of hospital stay • Readmission for AKI (within 2 weeks) • Health related quality of life (any measure)

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

The following methods were specific for this review:

(a) References that were excluded on sample size (N<80) from the guideline in 2013 for this review question were added back in if they were excluded only on the basis of a sample size N<80 to ensure consistency between the new data set and the original data set.

(b) Included RCTs reported CI-AKI using different definitions and different time points:

(c) Table 34 in appendix P shows a list of reported CI-AKI definitions. Some RCTs reported on more than one CI-AKI definition. A ranked list of CI-AKI definitions was developed to prioritise data extraction with the result that only one definition was extracted per trial. The prioritisation was based on committee discussions about which definitions were most clinically useful and the frequency of reporting using each definition in the included RCTs. See appendix B for the prioritisation of CI-AKI definitions. The committee agreed that

RCTs reporting different CI-AKI definitions could be analysed together as all these definitions were indicative of CI-AKI.

(d) RCTs reported CI-AKI events at different time points ranging from 1 to 5 days. The committee agreed that RCTs reporting different time points could be analysed together as long as the longest time point was 5 days or less.

(e) Included RCTs also reported different regime, duration, and volume (or dosage in the case of NAC) for most of the interventions. Details of included interventions are reported in appendix D clinical evidence tables. The committee agreed that RCTs could be analysed together grouping different regimes, durations, and volumes/dosage within a type of fluid:

- sodium chloride 0.9% (IV)
- no (intravenous) hydration
- sodium bicarbonate (IV)
- sodium chloride 0.45% (IV)
- sodium citrate (oral)
- oral fluids
- sodium bicarbonate (oral) + oral fluids
- sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
- NAC (oral) + sodium chloride 0.9% (IV)
- NAC (oral) + sodium bicarbonate (IV)
- sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
- NAC (IV) + sodium chloride 0.9% (IV)
- NAC (oral) + sodium chloride 0.45% (IV)
- NAC (IV) + sodium chloride 0.45% (IV)
- NAC (oral)
- NAC (IV bolus & oral) + sodium chloride 0.9% (IV)
- NAC (IV bolus) + sodium chloride 0.9% (IV)

(f) Some studies reported serum creatinine in mg/l, but the committee highlighted that µmol/l is the preferred unit of meausure in the UK. Therefore, any data on serum creatinine reported in mg/l were converted to the preferred measure µmol/l by multiplying mg/l by 88.4.

(g) Chen 2008 recruited 2 groups based on their baseline serum creatinine (group 1: serum creatinine <132.6µmol/l; group 2: serum creatinine ≥132.6µmol/l). Group 1 was allocated to sodium chloride 0.45% or no (intravenous) hydration. Group 2 was allocated to oral NAC + sodium chloride 0.45% or oral NAC. Therefore, Chen 2008 was split as 2008a and 2008b in the NMA data.

(h) Aslanger 2012 stated that sodium chloride 0.9% was given to all participants but the authors did not specify whether this fluid was given pre and/or post contrast. We assumed that the fluid was given at both pre and post contrast because the fluid was given for 12 hours and all people were given contrast within 12 hours of symptom onset, therefore all fluid must have continued after the contrast.

(i) Adverse events were extracted as number of people with adverse events rather than number of events to enable pooling of RCTs reporting on adverse events. Data was not extracted from RCTs only reporting number of events.

(j) The NMA models for a dichotomous outcome were based on models from the NICE Decision Support Unit (DSU) technical support document 2 (models 1c and 1d). The models are shown in appendix Q.

(k) Results were reported as the posterior median and 95% credible interval from the NMA models with the best fit to the data based on the NICE Guideline Updates team criteria for model choice detailed in appendix B.

(l) The DSU code presents the results of dichotomous outcomes as OR. These were converted to RR by the NICE Guideline Updates Team. Relative effects calculated on a log(odds ratio) scale were re-expressed as relative risks using the absolute probability of CI-AKI (25/250) from the sodium chloride 0.9% + oral NAC arm of Maioli et al. (2008). This study was selected to provide the baseline probability as it is a relatively large, European study that also reports results that are used to estimate the consequences of CI-AKI in the HE model; therefore, using this baseline probability allows for a consistent chain of evidence.

(m) Where the data for the NMA for CI-AKI (dichotomous outcome) included RCTs with 0 events in both arms, these RCTs were not included as part of the analysis because RCTs with 0 events in both arms do not contribute evidence on the relative treatment effects in pairwise meta-analysis or NMA.

(n) CI-AKI was reported as defined by study in pairwise analysis (usually 48-72 hours but diagnosed within 7 days of contrast being given to allow for delays in testing). For the NMA, number of diagnoses of CI-AKI within 5 days of the contrast being given was selected as the most appropriate outcome to prioritise because there were sufficient numbers of trials to form a connected network that included the majority of interventions.

(o) Inconsistency checking of the NMA was carried out (see Appendix R –NMA inconsistency checks).

(p) Although there were studies at high risk of bias included in the NMA, sensitivity analyses excluding these studies were not carried out because sensitivity analyses for the pairwise data did not alter the interpretation of the effects of the treatments with 2 exceptions (oral NAC + sodium chloride 0.45% compared to sodium chloride 0.45%; oral NAC + sodium chloride 0.9% compared to oral NAC + sodium bicarbonate). These were not considered sufficient to warrant running NMA sensitivity analyses for the CI-AKI outcome. See section on 'The quality of the evidence' for more information about the differences in interpretation between the analysis including all studies and the sensitivity analysis removing studies at high risk of bias.

We would like to acknowledge the Technical Support Unit, at University of Bristol, particularly Nicky Welton and Caitlin Daly, for providing advice, models, inconsistency checking and quality assurance for the network meta-analysis included in this review.

Clinical evidence

Included studies

A systematic search was carried out to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, which found 592 references (see appendix C for the literature search strategy). Evidence identified in the original guideline (37 references), excluded references in the original guideline with sample size <80 participants (20 references). References from the NICE surveillance review (29 references), and from systematic reviews (see below) were also reviewed.

In total, 647 references were identified for screening at title and abstract level with 490 excluded at this level. Full texts were ordered to be screened for 157 references (43 systematic reviews and 114 RCTs).

Forty-three systematic reviews were identified in the full text screen. There were 6 network meta-analyses published between 2017 and 2019. None of these network meta-analyses matched the question under consideration here and so a de novo NMA was carried out. The existing network meta-analyses were used as additional sources of references (10 RCTs). In total 75 references (reporting on 70 RCTs) were included based on their relevance to the

review protocol (appendix A). The clinical evidence study selection is presented as a PRISMA diagram in appendix D.

See appendix O for a list of references for included studies.

Excluded studies

See appendix M for a list of excluded studies with reasons for exclusion and appendix O for the bibliographic reference.

Table 2: Summary of clinical studies included in the evidence review

Short Title	Population	Interventions	Comparator	Outcome measure(s)
Adolph (2008) n = 145	• Undergoing elective diagnostic or interventional angiography • Age ≥18 years • Serum creatine *Two sCr levels >106µmol/l within 12 weeks of angiography that differed by <5%*	• IV sodium chloride 0.9%	• IV sodium bicarbonate	• Contrast induced AKI *Increase in sCr ≥25%* • CKD progression • Mortality • Number of patients needing RRT • Adverse events • Length of hospital stay (days) • Readmission for AKI • Health related quality of life
Agrawal (2004) n = 25	• Undergoing coronary angiography and/or percutaneous coronary intervention • Renal insufficiency as defined by a serum Cr ≥1.5 mg/dl or creatinine clearance ≤50 ml/min • Age ≥18 years	• Oral NAC + sodium chloride 0.9% *Pre-contrast: oral NAC 800 mg 12h prior angiography, 600 mg 2h prior angiography, with IV sodium chloride 0.45% 1 ml/kg for 12h before and during angiography. Post-contrast: oral NAC 600 mg 6h after angiography, with IV sodium chloride 0.45% 1 ml/kg for 12h after angiography (unless there was concern that this might precipitate*	• Placebo + IV sodium chloride 0.9% *Pre-contrast: matching placebo, with IV sodium chloride 0.45% 1 ml/kg for 12h before and during angiography. Post-contrast: matching placebo, with IV sodium chloride 0.45% 1 ml/kg for 12h after angiography (unless there was concern that this might precipitate*	• Contrast induced AKI *Either a 0.5-mg/dl increase in serum creatinine concentration or a 25% increase in serum creatinine concentration at 48 h*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		pulmonary edema).	*pulmonary edema).*	
Akyuz (2014) n = 225	• Undergoing coronary angiography and/or percutaneous coronary intervention • Age ≥70 years • Type 2 diabetes mellitus • History of chronic heart failure or systolic dyfunction • Anaemia • Hyper uricaemia	• Oral hydration *Encouraged to drink as much spring or tap water before procedure 12 - 2 hours before procedure*	• IV sodium chloride 0.9%	• Contrast induced AKI *>25% relative or ≥0.5 mg/dl increase in SCr* • Mortality • Number of patients needing RRT *Requiring dialysis within 30 days post procedure* • Adverse events
Albabtain (2013) n = 243	• Undergoing coronary angiography or PCI • Age ≥18 years • CIN *At risk of CIN, defined as having one of the following criteria on admission: serum creatinine ≥1.3 mg/dL (115 mmol/L) or were on diabetes mellitus medication.*	• Oral NAC + sodium chloride 0.9% *NAC orally 600 mg twice daily for 2 days starting the evening before the procedure. Ascorbic acid, supplied as effervescent tablets, 3 g 2 hours before the angiogram, 2 g after the angiogram, and 2 g 24 hours after the angiogram*	• IV sodium chloride 0.9% *Normal saline was started in all patients at a rate of 50 to 125 mL/h IV from the time of randomization until at least 6 hours after the procedure*	• CIN *Development of CIN or its definition components as measured 4–5 days after procedure. CIN was defined by an absolute increase of serum creatinine concentration of at least 0.5 mg/dL or a relative decrease of creatinine clearance of at least 25% from the baseline value measured 4 to 5 days after procedure*
Allaqaband (2002) n = 85	• Undergoing cardiovascular interventions requiring radio contrast • Serum creatinine *baseline creatinine ≥ 136.8*	• Oral NAC + IV sodium chloride 0.45% *Pre-procedure 600mg twice daily in the day before procedure and continuing throughout day of*	• IV sodium chloride *Pre-procedure 0.45% sodium chloride 1ml/kg/hr for 12 hours prior to procedure.* *Post-contrast: 0.45% sodium*	• Contrast induced AKI *at 48 hours, defined as absolute increase in serum creatinine level of at least 44.2 umol/L*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	umol/L or an estimated creatinine clearance of ≤60 ml/min • Other *scheduled to undergo cardiovascular interventions requiring the use of radio contrast*	*procedure, with 0.45% sodium chloride 1ml/kg/hr for 12 hours prior to procedure. Post-contrast: 0.45% sodium chloride 1ml/kg/hr for 12 hours.*	*chloride 1ml/kg/hr for 12 hours.*	
Aslanger (2012) n = 220	• Undergoing coronary angiography • Age ≥30 days • Other *Patients with STEMI undergoing coronary angiography within 24h of symptom onset*	• IV NAC + oral NAC + sodium chloride 0.9% *Pre-procedure: single IV bolus NAC of 1200mg during the procedure . (total 6g) Post-procedure: 1200mg NAC orally twice daily for 48h after the procedure. * IV saline 0.9% given as at 1ml/kg/hour for 21 hours (unclear whether this is pre, peri, or post-procedure)*	• Sodium chloride 0.9% *Pre-procedure: iv saline bolus of 12 ml during the procedure Post-procedure: placebo capsules for 48h after procedure. * IV saline 0.9% given as at 1ml/kg/hour for 21 hours (unclear whether this is pre, peri, or post-procedure)*	• Contrast induced AKI *at 72 hours, defined as increase in sCr ≥25% or 44µmol/l)*
Baskurt (2009) n = 145	• Undergoing coronary diagnostic angiography • eGFR *between 30 and 60 mL min-1 1.73 m-2* • Chronic kidney disease *moderate degree chronic kidney disease*	• Oral NAC + IV sodium chloride 0.9% *Pre-contrast: oral NAC twice daily the preceding day and the day of angiography, with IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h before contrast exposure. Post-contrast: oral NAC none, IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h after contrast exposure.y*	•IV sodium chloride 0.9% *Pre-contrast: IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h before contrast exposure. Post-contrast: IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h after contrast exposure.*	• Contrast induced AKI *0.5 mg dL-1 absolute increase in serum creatinine level*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
Berwanger (2011) n = 2308	• Undergoing peripheral vascular angiography, coronary diagnostic angiography, and PCI • Received imaging *Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or PCI* • Moderate to high CIN risk *At least one risk factor for CIN: age >70 years, chronic renal failure (stable serum creatinine concentrations >132.6 µmol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction <0.45, or hypotension*	• Oral NAC + IV sodium chloride 0.9% *NAC: a dose of 1200 mg NAC was administered orally every 12 hours. Two doses before and two doses after the procedure.0.9% Sodium chloride: 1 mL/kg per hour, from 6 - 12 hours before to 6 - 12 hours after angiography*	• Placebo + IV sodium chloride 0.9% *placebo: administered orally every 12 hours, for 2 doses before and 2 doses after the procedure 0.9% Sodium chloride: 1 mL/kg per hour, from 6 - 12 hours before to 6 - 12 hours after angiography*	• Contrast induced AKI *a 25% elevation of serum creatinine above baseline between 48 and 96 hours after angiography.* • Mortality *Deaths and cardiovascular deaths at 30 days* • Adverse events *other serious adverse events* • Need for dialysis *at 30 days* • Composite outcome *Deaths or need for dialysis at 30 days*
Boucek (2013) n = 126	• Contrast procedure not specified *elective radiologic procedure with contrast medium* • Age ≥18 years • Serum creatinine *≥100 mmol/L* • Diabetes mellitus	• IV sodium chloride 0.9% *Sodium chloride: 154 mL of 5.85% sodium chloride to 846 mL of 5% glucose. 1 h immediately before (at the rate of 3 mL/kg/h; limited to a maximal amount of 330 mL) and for 6 hour following contrast (at 1 mL/kg BW/h;*	• IV sodium bicarbonate *154 mL of 8.4% sodium bicarbonate to 846 mL of 5% glucose 154 mL of 8.4% sodium bicarbonate to 846 mL of 5% glucose. 1 h immediately before (at the rate of 3 mL/kg/h; limited to a maximal amount*	• CKD progression *Development of end stage renal failure at one month* • Mortality *at one month* • Length of hospital stay • Need for dialysis • CIN *Serum creatinine increase of ≥25% and/or ≥44*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	• Received imaging *a planned procedure with intra-arterial or intravenous use of contrast*	*limited to a maximum of 660 mL)*	*of 330 mL) and for 6 hour following contrast (at 1 mL/kg BW/h; limited to a maximum of 660 mL)*	*mmol/L (0.5 mg/dL) within 2 days following administration of contrast*
Brar (2008) n = 353	• Undergoing coronary angioplasty • Age ≥18 years • eGFR *≤60 ml/min/1.73m2 AND one or more of: diabetes mellitus; history of congestive heart failure; hypertension; or age ≥75 years*	• Sodium bicarbonate	• Sodium chloride 0.9%	• Contrast induced AKI *at 72 hours, defined as increase in sCr of at least 44.2 umol/L or 25% over baseline* • Mortality *and time to death, up to 6 months* • Length of hospital stay • Renal failure *need for RRT* • Composite outcome *first occurrence of death, RRT, or a reduction in eGFR of at least 20% confirmed by at least 2 separate measurements between days 30 and day 180*
Briguori (2002) n = 183	• Undergoing elective coronary and/or peripheral angiography and/or angioplasty • Serum creatinine *Impaired renal function (serum creatinine concentration*	• oral NAC + IV sodium chloride 0.45% *Pre-procedure: 600mg NAC given twice daily on the day before and day of procedure, with 0.45% IV sodium chloride given at a dose of 1*	• IV sodium chloride 0.45% *Pre-procedure: 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours prior to procedure. Post-procedure: 0.45% IV sodium chloride given at*	• Contrast induced AKI *at 48 hours, defined as increase in serum creatinine concentration of ≥25% over baseline at 48 hours, or the need for dialysis*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	>106.8 umol/L and/or estimated CrCl <70ml/min • Other *undergoing elective coronary and/or peripheral angiography and/or angioplasty*	*ml/kg/hour for 12 hours prior to procedure. Post-procedure: 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.*	*a dose of 1 ml/kg/hour for 12 hours.*	• Renal failure *need for RRT*
Briguori (2007) n = 235	• Undergoing coronary and/or peripheral angiography and /or angioplasty • Age ≥18 years • Serum creatinine *stable sCr concentration ≥176.8 µmol/l and/or glomerular filtration rate <40 mL · min -¹· 1.73 m-²* • Other *Patients with CKD who underwent coronary and/or peripheral angiography and /or angioplasty*	• NAC + sodium bicarbonate *Pre-procedure: NAc given orally at a dose of 1200mg twice daily, the day before and on the day of the procedure, with 154 mEq/L IV sodium bicarbonate (in dextrose and H2O) given at a dose of 3 ml/kg 1 hour pre-procedure. Post-procedure: Sodium bicarbonate given at a dose of 1 mL/kg/hour during procedure and or 6 hours after.*	• NAC + sodium chloride 0.9% *Pre-procedure: NAc given orally at a dose of 1200mg twice daily, the day before and on the day of the procedure, with 0.9% sodium chloride given at a dose of 1 mL/kg body weight/ hr (0.5 mL/kg for patients with left ventricular ejection fraction <40%) for 12 hours prior to procedure. Post-procedure: 0.9% sodium chloride (same dosing as pre-procedure) given for 12 hours.*	• Contrast induced AKI *at 48 hours, defined as an increase in the sCr concentration ≥25% from the baseline value at 48 hrs after administration of the contrast* • Renal failure *need for RRT*
Caglar (2014) n = 100	• Undergoing coronary angiography • eGFR *30 to 60 ml/min/1.73m²*	• oral NAC + IV sodium bicarbonate *NAC dose: 600 mg p. o. twice daily. NAC given day before and day of coronary angiography. Sodium bicarbonate dose: sodium bicarbonate: 154 mL of 1000mEq/L*	• IV sodium bicarbonate *Sodium bicarbonate dose: 154 mL of 1000mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water. Volume: 3 ml/kg/h for 1 hour before the procedure, and 1 ml/kg/h*	• Mortality • Adverse events *major adverse cardiac events* • Need for dialysis • CIN *An absolute 0.5 mg/ dL increase in SCr levels 48 hours after*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		sodium bicarbonate to 846 mL of 5% dextrose in water. Sodium bicarbonate volume: 3 ml/kg/h for 1 hour before the procedure, 1 ml/kg/h during and for 6 hours after the procedure	*during and for 6 hours after the procedure.*	*administration of radiocontrast medium was considered as CIN*
Carbonell (2007) n = 216	• Undergoing coronary angiography • Other *High risk coronary patients (diagnosed with angina at rest or post-MI or received thrombolytic therapy with failed recanalization so the cardiac catheterisation was an emergency procedure) with normal renal function (serum cr <123.8 umol/L or CrCl of >60 ml/min) undergoing coronary angiography*	• IV NAC + IV sodium chloride 0.45% *Pre-procedure: 600mg IV NAC diluted in 50ml of 0.9% saline, given for 30 mins, twice daily, starting within 6 hours before procedure, with 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.*	• IV sodium chloride 0.45% *Pre-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.*	• Contrast induced AKI *at 48 hours, defined at acute increase in serum Cr of at least 25% or 44umol/L over baseline.* • Mortality *during hospital stay*
Carbonell (2010) n = 81	• Serum creatinine *chronic renal disease, defined as stable serum Cr ≥123.76 umol/L or <60ml/min CrCl* • Other *same as associated study (see Carbonell 2007 for full list of inclusion and exclusion criteria)*	• IV NAC + 0.45 sodium chloride *Pre-procedure: 600mg IV NAC diluted in 50ml of 0.9% saline, given for 30 mins, twice daily, starting within 6 hours before procedure, with 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours*	• 0.45% sodium chloride *Pre-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.*	• Contrast induced AKI *at 48 hours, defined at acute increase in serum Cr of at least 25% or 44umol/L over baseline.* • Mortality • Length of hospital stay • Renal failure

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.		• Need for RRT
Castini (2010) n = 156	• Undergoing non-emergency coronary angiography or PCI • Contrast induced AKI *at 5 days: defined as an increase in sCr ≥25% baseline, reported separately using the definition of an absolute increase in sCr ≥44.2 µmol/l* • Renal failure *need for RRT*	• oral NAC + sodium chloride 0.9% *pre-procedure: 600mg NAC Twice daily on day before and day of administration of contrast, IV sodium chloride at a dose of 1ml/kg/hour for 12 hours prior to procedure.Post-procedure: same dose as pre-procedure, for 12 hours.*	• Sodium chloride 0.9% *pre-procedure: IV sodium chloride at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: same dose as pre-procedure, for 12 hours.* • Sodium bicarbonate *pre-procedure: IV sodium bicarbonate 154ml of 100mEq/L in 846ml of 5% dextrose in H2O, at 3ml/kg for 1 hour immediately before contrast. Post-procedure: IV sodium bicarbonate at 1ml/kg/hour for 6 hours.*	• Contrast induced AKI *at 5 days: defined as an increase in sCr ≥25% baseline, reported separately using the definition of an absolute increase in sCr ≥44.2 µmol/l* • Renal failure *need for RRT*
Chen (2008) n = 936	• Undergoing PCI • Other *people with myocardial ischemia (angina or positive exercise treadmill) scheduled for elective PCI*	**<sCr of 132.6 umol/L** • Sodium chloride 0.45% *Pre-procedure: 0.45% sodium chloride given at a dose of 1ml/kg/hour 12 hours before angiogram. Post-procedure: sodium chloride 0.45% given at a dose of*	**≥sCr of 132.6 umol/L** • NAC + sodium chloride 0.45% *Pre-procedure: NAC given twice orally loading dose of 1200mg, with 0.45% sodium chloride given at a dose of 1ml/kg/hour, both 12 hours before angiogram. Post-*	• Contrast Induced AKI *at 48 hours, defined as an increase in sCr of over 44.2 umol/L* • Mortality *at 6 months* • Renal failure *need for RRT; haemofiltration*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		1ml/kg/hour for 6 hours. Patient characteristics were not reported per arm. • non-hydration *Pre-procedure: non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Post-procedure: non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Patient characteristics were not reported per arm.*	*procedure: NAC given immediately after angiogram, with sodium chloride 0.45% given at a dose of 1ml/kg/hour for 6 hours. Patient characteristics were not reported per arm.* • NAC + non-hydration *Pre-procedure: NAC given twice orally loading dose of 1200mg, with non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Post-procedure: NAC given immediately after angiogram, with non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Patient characteristics were not reported per arm.*	*performed if oligoanuria >48h despite administration of furosemide >1g iv per 24h*
Cho (2010) n = 91	• Undergoing elective diagnostic coronary angiography • Age ≥18 years • Serum creatinine *stable serum creatinine levels of at least 1.1 mg/dL or estimated creatinine*	• IV sodium chloride 0.9% *IV sodium chloride: 154 mEq/L. 3 mL/kg for 1 h pre-contrast and 1 mL/kg for 6 h post contrast* • IV sodium bicarbonate *IV sodium bicarbonate: 154*	• oral hydration with water *500 mL of water 4 h prior to contrast exposure and stopped 2 h prior to procedure. Then 600 mL of water post procedure.* • oral hydration with water + oral	• Mortality *in-hospital mortality* • Length of hospital stay • CIN *greater than 25% increase in serum creatinine from baseline or an absolute increase of 0.5 mg/dL from*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	clearance less than 60 mL/min • Received imaging *undergoing diagnostic, elective coronary angiogram* • Chronic kidney disease	*mEq/L. 3 mL/kg for 1 h pre-contrast and 1 mL/kg for 6 h post-contrast*	sodium bicarbonate *500 mL of water 4 h prior to procedure and stopped 2 h prior to contrast exposure oral sodium bicarbonate: 3.9 g (46.4 mEq) 20 min prior to contrast exposure. Then 600 mL of water and 1.95 g (30.4 mEq) of oral sodium bicarbonate 2 hours and 4 hours after the contrast exposure.*	*baseline at 72 hours following exposure to radiocontrast*
Chong (2015) n = 548	• Undergoing cardiac catheterisation with or without PCI • Age ≥21 years • eGFR *15 - 60 ml/min/1.73m²* • Other *scheduled to receive elective cardiac catheterisation with or without PCI, and able to receive pre-hydration for 12 hours*	• high-dose oral NAC + IV sodium chloride 0.9% *NAC: 2 tablets of 600 mg dissolved in approximately 250 mL of water. Twice a day for 3 consecutive days, starting from the day before cardiac catheterisation (to a total of 6 doses).* *Sodium chloride 0.9%: 154 mEq/L at a rate of 1mL/kg/h, for 12 h pre contrast and 6 hours post contrast* • high-dose oral NAC + abbreviated IV sodium bicarbonate	• Abbreviated IV sodium bicarbonate *abbreviated loading IV infusion of 154 mEq/L sodium bicarbonate in 5% dextrose solution: 3 mL/kg/h for 1 h before cardiac catheterisation, and 1 mL/kg/h during and until 6 h post-contrast*	• Mortality *30 day mortality* • Length of hospital stay • Need for dialysis • CIN *≥25% increase of serum Cr concentration or a ≥44 µmol/L (0.5mg/dL) increase in serum Cr within 48 h of cardiac catheterisation or PCI*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		1.2 g oral NAC and abbreviated loading IV infusion of 154 mEq/L sodium bicarbonate in 5% dextrose solution: 3 mL/kg/h for 12 h before cardiac catheterisation, and 1 mL/kg/h during and until 6 h post-contrast		
Durham (2002) n = 81	• Undergoing angiography • Age ≥18 years • Serum creatinine *baseline serum Cr >1.7mg/dL* • Other *referred for cardiac angiography (diagnostic or therapeutic procedures)*	• Oral NAC + IV sodium chloride 0.45% *Pre-procedure: 1200mg (2400mg total) dose of NAC (mixed with 6ml orange juice) 1 hour precontrast, with 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for 12 hours before procedure. Post-procedure: remaining NAC given over 3 hours, with 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for up to 12 hours.*	• IV sodium chloride 0.45% *Pre-procedure: 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for 12 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for up to 12 hours.*	• Contrast induced AKI *at 48 hours, defined as an incrase in serum Cr of 0.5mg/dl*
Ertuk (2014) n = 315	• Undergoing intra-arterial procedure: PCI, coronary angiography with or without PCI, "peripheral procedures", "others" • Age • eGFR *< 60 ml/min/1.73 m²*	• oral NAC + IV sodium chloride 0.9% *oral NAC: 1200 mg sachet every 12 h for 24 h before and 48 hours after procedure (a total of 3 days and a total dose of NAC, 7200mg)* *IV sodium chloride 0.9%: 1ml/kg/h for 12 h*	• IV sodium chloride 0.9% *Administered a rate of 1ml/kg/h for 12 h before and 12 h after the procedure*	• Mortality *Deaths and cardiovascular deaths at 30 days and 1 year* • Need for dialysis *at 30 days and 1 year* • CIN *an increase in the SCr or cystatin C concentration of at least 0.5mg/dl and/or at least 25% from the baseline value at*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		before and after the procedure • IV NAC + IV sodium chloride 0.9% *IV NAC: a dose of 2400mg within 1 h immediately before the procedure and followed by 4800mg within 4–6 h after the procedure (a total dose of NAC, 7200mg). IV sodium chloride 0.9%: 1ml/kg/h for 12 h before and after the procedure*		*48 h after administration of the contrast dye; AND increase in the SCr or cystatin C concentration of at least 0.3 mg/dl from the baseline value at 48 h after administration of the contrast dye; AND ncrease in the serum cystatin C concentration of at least 10% from the baseline value at 48 h after administration of the contrast dye. Definitions reported separately.* • Composite outcome *Death, cardiovascular death, and need for dialysis at 30 days and at 1 year*
Ferrario 2009 n = 200	• Undergoing elective and diagnostic coronary angiography • Age *18 years or older* • Other *creatinine clearance <55 ml/min; scheduled for elective coronary and/or peripheral angiography and/or angioplasty and had a stable renal function as documented by a small ±10% variation in serum*	• oral NAC + IV sodium chloride 0.9% *Pre-contrast: oral NAC twice daily the day before the procedure, with IV sodium chloride 0.9% 1 ml/kg/h 12-24 h. Post-contrast: oral NAC twice daily the day of the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 24 h.*	• Placebo + IV sodium chloride 0.9% *Pre-contrast: placebo (tablets containing glucose) the day before the procedure, with IV sodium chloride 0.9% 1 ml/kg/h 12-24 h. Post-contrast: placebo (tablets containing glucose) the day of the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 24 h.*	• Contrast induced AKI *increase of serum creatinine levels of 25% or more and/or 0.5 mg/dl or more* • Notes *No patient required renal replacement therapy and no patient died in hospital*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	creatinine pre-procedural values when compared to the outpatients values performed 3–30 days before the procedure			
Fung (2004) n = 91	• Undergoing coronary angiography or PCI • Serum creatinine *sCr 149 - 400µmol/l; 2 sCr measurements within one month of angiography with <15% change to confirm stable renal function* • Other *undergoing elective coronary angiography or PCI*	• NAC + sodium chloride *Pre-procedure: 400mg on the day before and day of procedure. IV sodium chloride 0.9% 100ml/hour for 12 hours Post-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours*	• Sodium chloride 0.9% *Pre-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours Post-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours*	• Contrast induced AKI *at 48 hours, increase in sCr ≥ 44µmol/l or reduction in GFR ≥25%); subgroup analysis given for patients with diabetes* • Adverse events *including allergic reaction, not including heart failure; clinical heart failure so could not complete sodium chloride infusion regimen* • Renal failure *Need for RRT*
Goldenberg (2004) n = 180	• Undergoing PCI or urgent coronary angiography in people with high likelihood of ad hoc PCI • Serum creatinine *calculated CrCl of <50ml/min (if person is without diabetes) or <100ml/min (if person has diabetes); any patient with an absolute serum*	• Oral NAC + IV sodium chloride 0.45% *Pre-procedure: first dose given 8pm night before procedure with subsequent doses at 8am and 8pm day of procedure (to a total dose of 6000mg). Alternatively, participants received the first dose at 8am and 8pm on the day of*	• IV sodium chloride 0.45% *IV 0.45% sodium chloride was given at a dose of 75ml/hour for 24 hours beginning at the time of enrolment.*	• Contrast induced AKI *At 48 hours, incidence of CIN: defined as increase in serum creatinine of at least 25%* • Mortality *in-hospital and at 6 months* • Renal failure *need for RRT (in hospital and at 6 months)*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	creatinine of >200 umol/L • Received imaging *previous diagnostic angiography undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI*	*the procedure (to a total dose of 4000mg). IV 0.45% sodium chloride was given at a dose of 75ml/hour for 24 hours beginning at the time of enrollment.*		
Gomes (2005) n = 156	• Undergoing coronary angiography or PCI • Other *haemodynamic instability before the procedure (systolic blood pressure ≤90 mm Hg or diastolic blood pressure ≤60 mm Hg), history of sensitivity to N-acetylcysteine*	• Oral NAC + IV sodium chloride 0.9% *Pre-contrast: oral NAC 600 mg orally twice a day 1 day before procedure (2 doses), with IV sodium chloride 0.9% 1 mL/kg/min 12 h before contrast. Post-contrast: oral NAC 600 mg orally twice a day 2 doses after the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 12 h after contrast..*	• Placebo + IV sodium chloride 0.9% *Pre-contrast: matching placebo, with IV sodium chloride 0.9% 1 mL/kg/min 12 h before contrast. Post-contrast: matching placebo, with IV sodium chloride 0.9% 1 ml/kg/h for 12 h after contrast.*	• Contrast induced AKI *increase in serum creatinine ≥44.2 mmol/l* • Mortality *in-hospital death* • Number of patients needing RRT *Need for haemodialysis* • Length of hospital stay *Reported as centiles*
Habib (2016) n = 105	• Undergoing coronary angiography and/or PCI • Received imaging *undergoing coronary angiography* • Moderate to high CIN risk *at least one risk factor for CIN: age >70 years, baseline*	• oral NAC + IV sodium chloride 0.9% *NAC: 1200 mg orally every 12 h over 48 hours, one dose before coronary angiography and three doses after coronary angiography (total dose of NAC, 4800 mg including intervention dose); 0.9%*	• IV sodium chloride 0.9% *0.9% saline: started just before injection of contrast media and continued for 12 h at a rate of 1.0 mL/kg/min after angiography*	• CIN *an increase in serum creatinine concentration of 0.5 mg/dL or ≥25% of the baseline value within 48 h after the procedure*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	creatinine level >1.5 mg/dL, heart failure, diabetes mellitus or contrast media volume >300 mL • Other *Ischaemic heart disease or peripheral vascular disease*	*saline: started just before injection of contrast media and continued for 12 h at a rate 1.0 mL/kg/min after angiography*		
Hafiz (2012) n = 320	• Undergoing diagnostic or interventional angiography • Age ≥18 years • Serum creatinine *sCr >141µmol/l in non-diabetics and >124µmol/l in diabetics or eGFR <50ml/min/1.73m 2(MDRD)* • Other *Patients with renal insufficiency scheduled for diagnostic or interventional angiography*	• NAC + Sodium chloride 0.9% *Pre-procedure: oral NAC 1200mg 2-12 h before procedure, with 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours. Post-procedure: NAC 1200mg for 6-12 hours, with 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours.* • NAC + sodium bicarbonate *Pre-procedure: oral NAC 1200mg 2-12 h before procedure, with sodium bicarbonate at a dose of 3ml/kg/h for 1 hour. Post-procedure: NAC 1200mg for 6-12 hours, with sodium bicarbonate at a dose of 1ml/kg/h for 6 hours.*	• Sodium chloride 0.9% *Pre-procedure: 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours. Post-procedure: 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours.* • Sodium bicarbonate *Pre-procedure: sodium bicarbonate at a dose of 3ml/kg/h for 1 hour. Post-procedure: sodium bicarbonate at a dose of 1ml/kg/h for 6 hours.*	• Contrast Induced AKI *at 48 hours, defined as an increase in sCr ≥25% or 44µmol/l*
Heng (2008) n = 77	• Undergoing Coronary angiography,	• oral NAC + IV sodium bicarbonate	• matching placebo + IV	• Adverse events *major adverse cardiac events (cardiac death,*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	ventriculography and angioplasty • Serum creatinine *stable serum creatinine concentrations defined as a difference lower than 0.1 mg/dl (8.8 µmol/l) between a serum creatinine level measured 1– 2 months before cardiac angiography and the baseline level measured within 24 hours before cardiac angiography* • eGFR *rate below 56 ml/min* • Received imaging *Patients scheduled for cardiac angiography either elective coronary angiography and/or percutaneous coronary intervention* • Chronic kidney disease	*NAC dose: 1,200 mg twice daily, given three times prior to contrast and once after:* *Sodium bicarbonate: 1.4% intravenously at a rate of 1 ml/kg of body weight/hour for 12 hours pre-contrast and 12 hours after*	sodium bicarbonate *Matching placebo: 1,200 mg twice daily, given three times prior to contrast and once after.* *Sodium bicarbonate: 1.4% intravenously at a rate of 1 ml/kg/hour for 12 hours pre-contrast and 12 hours after*	*nonfatal myocardial infarction (defined as > 0.3 times the upper limit of creatine kinase-MB levels), and acute congestive heart failure)* • Need for dialysis • CIN *increase in serum creatinine of ≥ 44.2 µmol/l (0.5 mg/dl) (criterion a), increase in serum creatinine ≥25% (criterion b), and decline in GFR of ≥ 5 ml/min, (criterion c) within 48 hours. Where alternative explanations for renal impairment had been excluded.*
Hsu (2007) n = 20	• Undergoing coronary angiography and/or angioplasty • Serum creatinine *baseline SCC ≥ 1.6 mg/dL or*	oral NAC + IV sodium chloride 0.45% *NAC dose: 600 mg/twice a day. 2 doses pre-contrast and 2 doses post contrast (total oral*	• matched placebo + IV sodium chloride 0.45% *Matched placebo dose: 600 mg/twice a day. Two doses before and after contrast.*	• Contrast induced AKI *at 48 and 72 hours, defined as defined as an increase of at least 25% of baseline in the SCr concentration*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	estimated creatinine clearance (CCR) < 40 mL/min, • Diabetes mellitus *and an elevated HbA1c* • Received imaging *Cardiac angiography and received a volume of radiocontrast (iohexol) greater than 1.5 mL/kg*	*NAC 1200mg daily for 2 days) Sodium chloride 0.45% dose: 1ml/kg/h. 12 hours prior to contrast and 12 hours post contrast.*	*Sodium chloride 0.45%: 1 mL/kg/h. 12 hours before contrast and 12 hours after contrast*	
Izani Wan Mohamed (2008) n = 180	• Undergoing coronary angiography • Age ≥18 years • Serum creatinine *creatinine clearance between 40 - 90 ml/min* • Received imaging *elective admission for coronary angioplasty*	• oral NAC + IV sodium chloride 0.45% *oral NAC dose: 600 mg twice daily for four doses (mixed with orange drink), starting 12 hours prior to contrast administration (total oral NAC 1200mg daily for 2 days). IV sodium chloride 0.45% dose: 1 ml/kg/hr 12 hours before and after contrast administration*	• IV sodium chloride 0.45% *IV sodium chloride 0.45% dose: 1 ml/kg/hr 12 hours before and after contrast administration*	• Adverse events • Need for dialysis • CIN *an increase in serum creatinine ≥ 25% from baseline*
Jaffery (2012) n = 398	• Undergoing coronary angiography or percutaneous coronary intervention. • Age ≥18 years • Other *Patients with acute coronary syndrome undergoing*	• IV NAC + sodium chloride 0.9% *IV NAC: 1200 mg bolus followed by 200mg /h for 24hrs (iv solution consisted of 6g NAC in 500ml of 5% dextrose solution in water)). IV sodium chloride*	• Sodium chloride 0.9% *IV sodium chloride 0.9%, "the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs".* **Unclear timing*	• Contrast Induced AKI *at 72 hours, increase in sCr ≥25% from baseline* • Mortality *at 30 days and in-hospital mortality*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	coronary angiography or percutaneous coronary intervention.	*0.9%, "the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs".*Unclear timing*		• Length of hospital stay *in days* • Renal failure *need for RRT*
Kama (2014) n = 107	• Undergoing CT scan • Age ≥18 years • Receiving imaging *Received contrast-enhanced CT as part of emergency care* • Moderate to high CIN risk *according to Mehran score for CIN* • Other *whose presentations and follow-up creatinine levels were obtained*	• IV NAC + IV sodium chloride 0.9% *Pre, during and after contrast: 150 mg/kg NAC in 1,000 mL of 0.9% NaCl at a rate of 350 mL/hour* • IV sodium decarbonate + IV sodium chloride 0.9% *Pre, during and after contrast: 150 mEq in 1,000 mL of 0.9% NaCl at a rate of 350 mL/hour*	• IV sodium chloride 0.9% *Pre, during and after contrast: 1,000 mL 0.9% NaCl infusion of 350 mL/hour*	• Contrast induced AKI *25% increase or a greater than 0.5 mg/dL (44 lmol/L) increase in the serum creatinine level, 48 to72 hours after the administration of contrast agent compared with the baseline creatinine measurement.* • Renal failure *Renal failure necessitating renal replacement therapy*
Kay (2003) n = 200	• Undergoing elective coronary angiography • Other *stable chronic renal impairment and stable sCr (sCr >106µmol/l, CrCl <60ml/min) undergoing elective coronary angiography with or without intervention*	• oral NAC + sodium chloride 0.9% *Pre-procedure: 600mg NAC twice daily, starting the day before and given for 3 doses. IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 12 hours. Post-procedure: 600mg NAC given for one dose. IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 6 hours.*	• Sodium chloride 0.9% *Pre-procedure: IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 12 hours. Post-procedure: IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 6 hours.*	• Contrast induced AKI *at 48 hours, increase in sCr ≥25% 48h after contrast administration* • Mortality *in hospital* • Adverse events *due to study drug – nausea causing discontinuation of study drug* • Length of hospital stay

Short Title	Population	Interventions	Comparator	Outcome measure(s)
				• Renal failure *need for RRT*
Khalili (2006) n = 70	• Undergoing elective abdominal or CT scanning • Serum creatinine *stable SCr during the 3 days prior to procedure* • Chronic kidney disease *known history of chronic kidney disease (serum creatinine [SCr] concentration above 106.1 umol/L or creatinine clearance [CrCl] of less than 60 ml/min)*	Oral NAC + IV sodium chloride 0.9% *Pre-procedure: NAC 1200mg once daily, on the day before imaging and at the day of contrast. 1000ml IV sodium chloride 0.9% given at a dose of 1ml/kg/hour prior to procedure.*	• IV sodium chloride 0.9% *Pre-procedure: 1000ml IV sodium chloride 0.9% given at a dose of 1ml/kg/hour prior to procedure.*	• Contrast induced AKI *at 48 and 72 hours, defined as defined as an increase of at least 25% of baseline in the SCr concentration*
Kitzler (2012) n = 20	• Undergoing elective diagnostic radiocontrast CT • Serum creatinine *> 1.25 mg/dL for males and 1.09 mg/dL for females* • Age ≥18 years	• oral NAC + IV sodium chloride 0.45% + placebo emulsion *NAC: granules 1200 mg, 12 and 6 hours before and 12 and 6 hours after contrast (total oral NAC 2400mg daily for 2 days sodium chloride 0.45%: 1 ml/kg/h 12 hours before and 12 hours after contrast placebo emulsion: 540 mg for 30 min (placebo for vitamin E). Received 12 and 6 hours before contrast and 6*	• placebo + IV sodium chloride 0.45% *Placebo granules: granules 1200 mg, 12 and 6 hours before and 12 and 6 hours after contrast Sodium chloride 0.45%: 1 ml/kg/h 12 hours before and 12 hours after contrast Placebo emulsion: 540 mg for 30 min (placebo for vitamin E). Received 12 and 6 hours before contrast and 6 and 12 hours after contrast.*	• CIN *an increase in serum creatinine of more than 25 % over the baseline value in the 48 h following CT scan*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		and 12 hours after contrast.		
Koc (2012) n = 220	• Undergoing coronary angiography and PCI • Age ≥18 years • Serum creatine *Creatinine clearance 60ml/min or less and/or baseline serum creatine level 1.1 mg/dL or more*	• IV NAC + IV sodium chloride 0.9% *IV bolus of 600 mg of NAC twice daily before and on the day of the coronary procedure (total=2.4 g) plus IV 0.9% saline 1 mL/ kg/h before, on and after the day of the coronary procedure*	• IV sodium chloride 0.9% *IV 0.9% saline 1 mL/kg/h before, on and after the day of coronary procedure*	• CIN *Alteration in SCr levels 48 hours after the administration of the contrast media. The secondary end point was the development of CIN after the procedure. CIN was described as a baseline SCr≥25% and/or an absolute increase in SCr of ≥0.5 mg/dL 48 hours after the procedure*
Kooiman (2014a) n = 548	• Undergoing CE-CT • Age ≥18 years • Chronic kidney disease *eGFR < 60 mL/min/1.73 m2 estimated by the Modification of Diet in Renal Disease formula and were eligible for the fluid challenge of saline hydration.*	• Sodium bicarbonate *250 mL intravenous 1.4% sodium bicarbonate 1 h prior to CE-CT without hydration post-CE-CT*	• IV sodium chloride 0.9% *2000 mL of 0.9% saline, 1000 mL prior to and 1000 mL post-CE-CT*	• Contrast induced AKI • Adverse events *Acute heart failure due to volume expansion* • Adverse events *Acute heart failure due to volume expansion* • Readmission for AKI *Rehospitalization or outpatient visit* • Renal failure *Recovery of renal function in CI-AKI patients [recovery defined as an increase in serum creatinine <25% or <44 µmol/L (0.5 mg/dL) measured at 2 months post-CE-CT compared with baseline* • Serum creatinine clearance

Short Title	Population	Interventions	Comparator	Outcome measure(s)
				relative increase in serum creatinine measured between 48 and 96 h post-CE-CT compared with baseline. • Need for dialysis
Kooiman (2014b) n = 139	• Undergoing CTPA • Age ≥18 years • Chronic kidney disease *eGFR < 60 mL min-1/1.73m2* • Other *High clinical suspicion of acute PE requiring CTPA were eligible for inclusion (IE Wells score >4 or Abnormal D-dimer)*	• IV sodium bicarbonate *Pre CTPA: 250 mL intravenous 1.4% sodium bicarbonate 1h* *Post-CTPA: Without hydration*	• No hydration *No hydration given*	• Contrast induced AKI *Incidence of CI-AKI* • Renal failure *Recovery of renal function in CI-AKI patients (increase in serum creatinine <25% or <44 umol L-1 measured at 2 months after CTPA compared with baseline* • Serum creatine clearance *Serum creatinine increase measured between 48 and 96 h after CTPA compared with baseline* • Need for dialysis
Kooiman (2018) n = 333	• Procedure varied between practices, including: angiography, digital substration angiography, percutaneous coronary intervention, endovascular aneurism repair, coronary angiography or percutaneous coronary intervention • Age ≥18 years • eGFR	• IV sodium bicarbonate *IV sodium bicarbonate*	• IV sodium chloride 0.9% *Peri-procedural intravenous hydration with 0.9% saline, 1000 ml in 4±12 hours prior to and 1000 ml in 4±12 hours following contrast administration (total volume 2000 ml).*	• Contrast induced AKI *incidence of CI-AKI (at 48±96 hours following contrast exposure).* • Readmission for AKI *Re-hospitalization and outpatient visits within 2 months follow-up*• • Renal failure *Recovery of renal function (i.e. no longer fulfilling the criteria of CI-AKI compared with baseline)*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	< 45 ml/min, or an eGFR 45±60 ml/min in combination with diabetes mellitus or at least two other risk factors for the development of CI-AKI (i.e. peripheral arterial disease, congestive heart failure, age > 75 years, anemia, use of diuretics or non-steroidal anti-inflammatory drugs)			• Serum creatinine clearance *relative increase in serum creatinine (%) measured once in the 48±96 hours following contrast exposure compared with baseline* • Need for dialysis
Kotlyar (2005) n = 65	• Undergoing coronary or peripheral angiography and/or stenting • Serum creatinine *serum creatinine ≥0.13 mmol/l;* • Received imaging *undergoing elective coronary, carotid or peripheral angiography and/or PTCA and stenting*	• IV NAC 300mg + IV sodium chloride 0.9% *NAC dose: 300mg prepared in 100 ml of 5% dextrose and administered over 20 min. 2 hours before contrast and 2 - 4 hours post contrast. IV sodium chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast* • IV NAC 600mg + IV sodium chloride 0.9% *NAC dose: 600mg prepared in 100 ml of 5% dextrose and administered over 20 min. 2 hours before contrast and 2 - 4 hours post contrast. IV sodium*	• IV sodium chloride 0.9% *IV sodium chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast.*	• Adverse events *clinical adverse events including allergic reaction to the study medication, need for haemodialysis and congestive cardiac failure* • CIN *an increase in the serum creatinine concentration of at least 0.044 mmol/l*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast.		
Lee (2011) n = 382	• Undergoing angioplasty • Serum creatinine *sCr ≥97.24 µmol/l* • Age ≥18 years • Diabetes mellitus *was defined as use of hypglycemic agents or insulin. Fasting plasma glucose >126mg/dl, or random plasma glucose ≥ 200mg/dl* • eGFR *Estimated GFR <60 ml/min/1.73m²* • Other *scheduled for elective coronary or endovascular angioplasty/ intervention*	• NAC + sodium bicarbonate *Pre-procedure: NAC 1200mg orally twice daily on the day before and the day of procedure. Sodium bicarbonate given at a dose of 154 mEq/L sodium bicarbonate in dextrose and water at 3ml/kg/hour for 1 hour before contrast. Post-procedure: Sodium bicarbonate given at a dose of 154 mEq/L sodium bicarbonate in dextrose and water at 1ml/kg/hour for 1 hour during contrast and 6 hours after.*	• NAC + sodium chloride *Pre-procedure: NAC 1200mg orally twice daily on the day before and the day of procedure. Sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours before contrast. Post-procedure: Sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours after contrast.*	• Contrast induced AKI *at 48 hours, defined as an absolute increase in the sCr concentration ≥44.2µmol/l* or ≥25% from the baseline value at 48 hrs after contrast exposure* • Mortality *cumulative rates at 6 months* • Renal failure *need for RRT*
MacNeill (2003) n = 57	• Undergoing elective cardiac angiography • Serum creatinine *serum creatinine (Cr) ≥ 1.5 mg/dl on the morning of the planned procedure*	• oral NAC + IV sodium chloride 0.45% *NAC dose: 2 doses of 600mg. 1 dose at randomization, 1 dose 4 h later pre-contrast. 3 doses at 12-h intervals post-contrast (total oral*	• placebo + IV sodium chloride 0.45% *Placebo: 1 dose at randomization, 1 dose 4 h later pre-contrast. 3 doses at 12-h intervals post-contrast. sodium chloride 0.45% dose: not*	• CIN *a rise in serum creatinine of > 25% from baseline to 72 hours*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	• Received imaging *undergoing elective cardiac catheterization*	*NAC 1200mg daily for 2 days and 600mg the 3rd day).sodium chloride 0.45% dose: not specified. 1 ml/kg/hr for 12 hr for in-patients and 2 ml/kg/hr for 4 hr for day-case patients pre-contrast. 75 ml/hr for 12 h post-contrast.*	*specified. 1 ml/kg/hr for 12 hr for in-patients and 2 ml/kg/hr for 4 hr for day-case patients pre-contrast. 75 ml/hr for 12 h post-contrast.*	
Maioli (2008) n = 502	• Undergoing coronary angiography • Serum creatinine *pre-angiographic estimated Cr clearance <60 ml/min* • Chronic kidney disease *chronic kidney dysfunction who underwent planned coronary angiographic procedures*	• NAC + sodium bicarbonate *Pre-procedure: NAC given at a dose of 1200mg twice daily, on the day before and day of procedure, IV sodium bicarbonate given at a dose of 154 mEq/l in dextrose and water, 3ml/kg for 1 hour before procedure. Post-procedure: IV sodium bicarbonate, 1 ml/kg/hour for 6 hours after procedure.*	• NAC + sodium chloride 0.9% *Pre-procedure: NAC given at a dose of 1200mg twice daily, on the day before and day of procedure, IV sodium chloride given at a dose of 1ml/kg/hour for 12 hours before procedure. Post-procedure: IV sodium chloride given at a dose of 1ml/kg/hour for 12 hours.*	• Contrast induced AKI *at 48 hours, CI-AKI was defined as ≥25% relative increase in baseline serum creatinine* • Mortality *at 10 days* • Renal failure *need for RRT*
Maioli (2011) n = 461	• Undergoing PCI • Age ≥18 years • Other *have had a STEMI and is a candidate for primary PCI*	• Sodium bicarbonate *Pre-procedure: sodium bicarbonate (154 mEq/L in dextrose and water) given as a bolus of 3 mL/kg of sodium bicarbonate solution in 1 hour, starting in the emergency room. Post-procedure: given as an infusion of 1 mL/kg per hour*	• No hydration *Unclear if no IV hydration only or no hydration at all*	• Contrast induced AKI *at 48 and 72 hours: at 48 and 72 hours: defined as an increase in serum creatinine of at least 25% or 44umol/L over baseline* • Mortality *In-hospital mortality* • Renal failure *need for RRT*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		for 12 hours. Mean total volume: 1157 (SD 228) ml. • Sodium chloride 0.9% *Post-procedure only: given at a dose of 1ml/kg/hour for 12 hours after procedure.*		
Marenzi (2006) n = 354	• Undergoing echocardiogram within 24h of admission • Other *ST-segment elevation acute MI presented within 12h after onset (18h in case of cardiogenic shock)of symptoms*	• IV NAC + IV sodium chloride 0.9% *Pre-procedure: single IV bolus Post-procedure: twice daily for 48 hours, 0.9% sodium chloride 1ml/kg/h IV for 12 hours* • IV NAC + IV sodium chloride 0.9% *Pre-procedure: single IV bolus Post-procedure: twice daily for 48 hours, 0.9% sodium chloride 1ml/kg/h IV for 12 hours*	• IV sodium chloride *Pre-procedure: not reported Post-procedure: 0.9% sodium chloride 1ml/kg/h IV for 12 hours*	• Contrast induced AKI *at 48 and 72 hours* • Mortality *in-hospital* • Renal failure *need for RRT* • Serum creatinine clearance *increase in serum creatinine of at least 25% at 72h over baseline*
Martin-Moreno (2015) n = 167	• Undergoing computed tomography • Age ≥18 years • eGFR *≥ 30 ml/min/1.73 m2* • Other *Hospitalised for at least 48 h*	• IV sodium bicarbonate *Pre-procedure: 1/6 molar 3 ml/kg/h, 1 hour pre-procedure Post-contrast: none* • oral sodium citrate *Pre-contrast: 1,380 mg/l of sodium 75 ml/10 kg, divided into 4*	• no (intravenous) hydration *Pre-contrast: no prophylaxis for CI-AKI Post-contrast: none*	• Contrast Induced AKI *Serum creatinine of ≥ 25% from baseline within 24 h after contrast administration*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
		doses (1 dose per hour), 4 hours pre-procedure *Post-contrast: none*		
Masuda (2007) n = 61	• Undergoing emergency diagnostic or interventional coronary procedure • Age ≥20 years • Other *Renal dysfunction (serum creatinine concentration >1.1 mg/dl or estimated glomerular filtration rate <60 ml/min)*	• IV sodium bicarbonate *154 mEq/L sodium bicarbonate. 3 ml/kg/hour before the coronary procedure. 1 ml/kg/hour during and 6 hours after the procedure*	• IV sodium chloride 0.9% *154 mEq/L sodium chloride. 3 ml/kg/hour before the coronary procedure. 1 ml/kg/hour during and 6 hours after the procedure*	• Contrast induced AKI *Increase >0.5 mg/dl or >25% in serum creatinine concentration within 2 days of the procedure* • Mortality *2008 study* • Number of patients needing RRT *Maintenance dialysis or kidney transplant* • Adverse events
Masuda (2008)	Associated study of another trial (Masuda 2007)			
Merten (2004) n = 137	• Age ≥18 years • Serum creatinine *Stable sCr ≥97.2µmol/l*	• Sodium bicarbonate	• Sodium chloride	• Contrast induced AKI *CI-AKI at 48 hours (increase in sCr ≥25%)* • Mortality • Number of patients needing RRT • Adverse events • Length of hospital stay *y "All individuals with CI-AKIexperienced*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
				prolonged hospitalisation…". No other information reported. • Notes *Change in MAP after initial bolus Urine pH after initial bolus Change in serum bicarbonate on day 1 Change in serum potassium on day 1 Change in serum Creatinine (highest level day 1or 2 used) Change in estimated GFR*
Miner (2004) n = 180	• Undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI • Serum creatinine *Patients without diabetes and a calculated creatinine clearance of <50 mL/min, Patients with diabetes and a calculated creatinine clearance of <100mL/min, Any patient with an absolute serum creatinine of > 200µmol/L* • Other *previous diagnostic*	• Oral NAC + sodum chloride 0.45% *Pre-procedure: 2000mg oral NAC, first dose 8pm the night before the procedure with subsequent doses at 8am and 8pm the day of their procedure. Same day patients received their first dose at 8am and 8 pm on the same day. (prior day patients received a total of 6000mg and same day patients a total of 4000mg). IV sodium chloride 0.45% was given for 75ml/hour for*	• IV sodium chloride 0.45% *IV sodium chloride 0.45% was given for 75ml/hour for 24 hours from the time of enrollment.*	• Contrast induced AKI *at 48 hours, defined as planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI. reduction in CI-AKI was limited to those patients enrolled the day prior to the procedure.* • Mortality *in-hospital and at 6 months* • Number of patients needing RRT

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	angiography undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI	*24 hours from the time of enrollment.*		*in-hospital and at 6 months*
Motohiro (2011) n = 158	• Undergoing coronary angiography or intervention • Age ≥20 years • eGFR *<60ml/min/1.73m²* • Other *undergoing coronary angiography or intervention*	• Sodium bicarbonate + sodium chloride 0.9% *Pre-contrast: Sodium bicarbonate (1000 mEq/L to 846ml of 5% dextrose in water) given at a dose of 1ml/kg/hour for 3 hours, with sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours pre-procedure.Post-procedure: Sodium bicarbonate (same dose as above) given for 6 hours and sodium chloride (same dose as above) for 12 hours.*	• Sodium chloride 0.9% *Pre-contrast: sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours pre-procedure. Post-procedure: sodium chloride (same dose as above) for 12 hours.*	• Contrast induced AKI *at 48 hours, defined as an Absolute increase in the sCr concentration of ≥44.2µmol/l* or as a 25% increase from the baseline value at 48 hrs after contrast exposure*
Mueller (2002) n = 1620	• Undergoing elective or emergency coronary angioplasty • Received imaging *people with myocardial ischemia (angina or positive exercise treadmill) scheduled for elective PCI*	• IV sodium chloride 0.9% *IV sodium chloride 0.9% dose: 154mmol/L at rate of 1ml/kg/h. From 8 am on day of procedure till 8am the following day (mean total fluid 2022ml).*	• IV sodium chloride 0.45% *IV sodium chloride 0.45% dose: in 5% glucose, 77mmol/L of sodium chloride at a rate of 1ml/kg/h. From 8 am on day of procedure till 8am the following day (mean total fluid: 2028ml).*	• Mortality *at 30 days* • Adverse events *Major adverse cardiac events within 30 days, defined as death, myocardial infarction, urgent target vessel revascularisation, or hospitalisation for unstable angina; Peripheral*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
				vascular complications defined as false aneurysms requiring surgery, compression or bleeding requiring surgery or transfusion • Length of hospital stay • Need for dialysis *during hospitalisation* • CIN *an increase in serum creatinine concentration of at least 0.5 mg/dL (44 µmol/L) within 48 hours*
Nijssen (2017) n = 660	• Undergoing CT scan • Age ≥18 years • eGFR *Estimated glomerular filtration rate (eGFR) between 45 and 59 mL per min/1·73 m² combined with either diabetes, or at least two predefined risk factors (age >75 years; anaemia defined as haematocrit values <0·39 L/L for men, and <0·36 L/L for women; cardiovascular disease; non-steroidal anti-*	• IV sodium chloride 0.9% *Pre-procedure: prophylactic intravenous 0·9% NaCl 3–4 mL/kg per hour during 4 h before. Post-procedure: same again, for 4 hours. When deemed necessary, the physician could choose to instead administer long protocol intravenous 0·9% NaCl 1 mL/kg per h during 12 h before and 12 h after contrast administration.*	• No hydration *No prophylactic hydration given*	• Adverse events *Major adverse events were defined as all-cause mortality, renal replacement therapy, intensive care admission, and sequelae of fluid administration. Major renal adverse events were defined as renal failure (defined as eGFR <15 mL per min/1·73 m²), renal decline with >10 eGFR units, renal decline to eGFR lower than 30 mL per min/1·73 m², or a combination of the latter two, at*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	inflammatory drug or diuretic nephrotoxic medication); or eGFR between 30 and 45 mL per min/1·73 m²; or multiple myeloma or lymphoplasmacytic lymphoma with small chain proteinuria.			*26–35 days. Clinical sequelae of fluid administration included symptomatic heart failure, hypernatraemia or hyponatraemia, and supraventricular or ventricular arrhythmias.* • Serum creatine clearance *Mean change in serum creatinine from baseline at 2–6 and 26–35 days after contrast administration* • CIN *Defined as the between-group difference in proportion of patients with an increase in serum creatinine by more than 25% or 44 µmol/L23 within 2–6 days of contrast exposure, and costeffectiveness of no prophylaxis compared with intravenous prophylactic hydration in the prevention of contrast-induced nephropathy*
Oldemeyer (2003) n = 96	• Undergoing coronary angiography • Age ≥19 years • Serum creatinine *baseline calculated*	• oral NAC + IV sodium chloride 0.45% *Pre-procedure: 1500mg NAC given orally in 120 ml of carbonated beverage, using*	• IV sodium chloride 0.45% *Pre-procedure: 1IV 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours. Post-*	• Contrast induced AKI *at 48 hours, absolute increase in serum creatinine of ≥0.5mg/dl or a relative increase*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	creatinine clearance <50ml/min; Serum creatinine >1.2mg/dl • Other *referred for elective coronary angiography; anticipated use of at least 75ml of contrast.*	*the 10% acetylcysteine inhalation solution starting the evening before angiography and every 12 hours for 4 doses. IV 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.Post-procedure: 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.*	*procedure: 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.*	*of ≥25% in serum creatinine compared to baseline* • Length of hospital stay • Renal failure *need for RRT*
Poletti (2007) n = 87	• Undergoing CT scan • Serum creatinine *Serum Cr >106 umol/L* • Received imaging *emergency CT needed within 12 hours of admission*	• IV NAC + IV sodium chloride 0.45% *Pre-contrast: 900mg of NAC diluted in a 50ml solution of 5% glucose, with 0.45% sodium chloride given at a dose of 5ml/kg for 1 hour. Post-contrast: 900 mg NAC minxued into 0.45% sodium chloride perfusion at a dose of 1ml/kg/hour for 12 hours*	• IV sodium chloride 0.45% *Pre-contrast: 0.45% sodium chloride given at a dose of 5ml/kg for 1 hour. Post-contrast: 0.45% sodium chloride perfusion at a dose of 1ml/kg/hour for 12 hours*	• Contrast induced AKI *at least 25% increase in serum Cr over baseline*
Rashid (2004) n = 94	• Undergoing angiography or angioplasty • Serum creatinine *subgroup analysis also presented for normal vs. raised serum creatinine* • Other *patients with vascular disease undergoing elective*	• IV NAC + IV sodium chloride 0.9% *IV NAC: 1000mg IV given in the bag of sodium chloride 0.9% pre and post procedure. Sodium chloride: 0.9% 500ml given 6-12 hours pre-procedure given for 4-6 hours and immediately post-*	• IV sodium chloride *Sodium chloride: 0.9% 500ml given 6-12 hours pre-procedure given for 4-6 hours and immediately post-procedure for 4-6 hours.*	• Contrast induced AKI *at 48 hours: defined as increase in serum creatine of 44.2 umol/L or 25% over baseline* • Mortality *at 7 days* • Renal failure *requiring RRT*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	angiography or angioplasty	*procedure for 4-6 hours.*		
Reinecke (2007) n = 424	• Undergoing coronary angiography • Serum creatinine *sCr 114.9 - 309.4 umol/L* • Other *admitted for elective left heart catheterization*	• Oral NAC + sodium chloride 0.9% *Pre-procedure: 600mg oral NAC one dose the evening before procedure and another dose the morning before procedure, IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours Post-procedure: one dose the evening after procedure and another dose the morning the day after procedure, IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours*	• Sodium chloride 0.9% *Pre-procedure: IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours Post-procedure: IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours*	• Contrast induced AKI *at 24 and 72 hours, and at 30-60 days; defined as an increase in enzymaticaly determined sCr of at least 44.2 umol/L* • Mortality *in-hospital and 30 day mortality* • Adverse events *relevant bleeding (loss in hemoglobin of 2g/dl or more)* • Renal failure *in-hospital haemodialysis due to oliguria or uremia*
Sadineni (2017) n = 95	• Undergoing nonemergent coronary angiography and percutaneous coronary interventions • Age ≥30 years • Serum creatinine *≥1.2 mg/dl on most recent sample drawn within 3 months of planned procedure* • Received imaging	• oral NAC + IV sodium chloride 0.9% *oral NAC dose: 600 mg twice daily. one day before and after the procedure (total 1200mg daily for two days).* *IV sodium chloride 0.9%: 0.5 ml/kg/h. 12 hours before and 12 hours after the procedure.*	• IV sodium chloride 0.9% *IV sodium chloride 0.9%: 0.5 ml/kg/h. 12 hours before and 12 hours after the procedure*	• Mortality • Need for dialysis • CIN *Either a relative increase in serum creatinine from baseline of ≥25% or an absolute increase of ≥0.3 mg/dl (44.2 µmol/L) during days 1 and 2 post-contrast*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	Patients undergoing clinically driven nonemergent coronary angiography and percutaneous coronary interventions for both stable and unstable patients with angina, non-ST-segment elevation myocardial infarction (NSTEMI) and acute myocardial infarction/STEMI			
Saitoh (2011) n = 14	• Undergoing elective diagnostic CAG • Serum creatinine *serum creatinine ≥1.5 mg/dl and/or creatinine clearance <60 ml/min*	• Oral NAC + IV sodium chloride 0.9% *Pre-contrast: oral NAC 704 mg twice daily 1 day before CAG for a total of 2 days, with IV sodium chloride 0.9% 1 ml/kg/h 12 h before the administration of contrast. Post-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h after CAG.*	• IV sodium chloride 0.9% *Pre-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h before the administration of contrast. Post-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h after CAG.*	• Contrast induced AKI *increase in serum creatinine level by at least 0.5 mg/dl and/or 25%*
Seyon (2007) n = 40	• Serum creatinine *Baseline ≥115 µmol/l (1.4 mg/dL) for males or equal to or greater than 115 mol/L (1.3 mg/dL) for females* • Age ≥18 years • Other *Diagnosis of acute coronary syndrome,*	• Oral NAC + IV sodium chloride 0.45% *NAC: 600 mg four times daily. First dose at 8 am the day of the procedure and 3 doses after coronary angiography with the first dose at 8 pm Sodium chloride 0.45%: 1 ml/kg/hour*	• Placebo + IV sodium chloride 0.45% *Placebo: Four times daily. First dose at 8 am the day of the procedure and 3 doses after coronary angiography with the first dose at 8 pm Sodium chloride 0.45%: 1 ml/kg/hour*	• Contrast induced AKI *Absolute increase in serum creatinine of 44 mol/L (.5 mg/dL) within 48 hours of contrast media exposure and/or a relative increase in serum creatinine of 25% above baseline within 48 hours of*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	scheduled for coronary angiography with or without concomitant PCI; Creatine clearance less than 50 ml/min			*contrast media exposure*
Shyu (2002) n = 121	• Undergoing cardiac angiography • Serum creatinine *Serum creatinine >176.8 µmol/l and <530.4 µmol/l; Rates of creatinine clearance < 40 ml/min and >8 ml/min; history of chronic renal failure with a stable serum creatinine concentrations (A difference of ≤0.1 mg/dl between baseline serum creatinine at 12 - 24 hrs before coronary angiography and serum creatinine measured 1-2 weeks before angiography)*	• Oral NAC + sodium chloride 0.45% *Pre-procedure: 400mg NAC twice daily for a day prior to and day of procedure. IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure.Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure.*	• Sodium chloride 0.45% *Pre-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure.*	• Contrast induced AKI *at 48 hours, increase in serum creatinine of at least 44.2 µmol/l at 48 hrs after contrast*
Solomon (2015) n = 391	• Undergoing angiography • Age ≥18 years • eGFR *<45 ml/min per 1.73m2* • Other *scheduled for elective coronary or peripheral angiography*	• Sodium bicarbonate *Pre-procedure: 1.3% sodium bicarbonate (154 mEq/L) given at 5ml/kg over 1 hour. post-procedure: 1.5 ml/kg per h during and for 4 h after angiography*	• Sodium chloride 0.9% *Pre-procedure: 154 mEq/L sodium chloride 0.9% given at 5ml/kg over 1 hour. post-procedure: 1.5 ml/kg per h during and for 4 h after angiography*	• Contrast induced AKI *at 72 hours, defined as increase in sCr of at least 44.2 umol/L or 25% over baseline* • Mortality *and time to death, up to 6 months*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
				• Length of hospital stay • Renal failure *need for RRT* • Composite outcome *first occurrence of death, RRT, or a reduction in eGFR of at least 20% confirmed by at least 2 separate measurements between days 30 and day 180*
Tamura (2009) n = 144	• Undergoing arteriography or PCI • Age ≥20 years • Serum creatinine *sCr >97.24 to <176.8 umol/L*	• Sodium bicarbonate + sodium chloride 0.9% *Pre-procedure: sodium bicarbonate given as a single 20mEq IV bolus, 5 minutes before contrast. Sodium chloride 0.9% given at a dose of 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) for 12 hours prior to contrast procedure.Post-procedure: Sodium chloride 0.9% (same dose as pre-procedure) for 12 hours.*	• Sodium chloride 0.9% *Pre-procedure: Sodium chloride 0.9% given at a dose of 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) for 12 hours prior to contrast procedure. Post-procedure: Sodium chloride 0.9% (same dose as pre-procedure) for 12 hours.*	• Contrast induced AKI *at 72 hours defined as increase in sCr of >44.2umol/L or >25% increase from baseline.* • Mortality *at 7 days* • Renal failure *Need for RRT*
Tepel (2000) n = 83	• Undergoing elective CT • Serum creatinine *sCr > 106 µmol/L; CrCl < 50ml/min; also need to have*	• Oral NAC + sodium chloride 0.45% *Pre-procedure: 600mg NAC given twice daily, day before and on*	• Sodium chloride 0.45% *Pre-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12*	• Contrast induced AKI *at 48 hours, defined as an increase in the serum creatinine 0.5 mg per*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	a history of chronic renal failure and with stable serum creatinine concentrations. • Other *underwent elective CT for the evaluation of an abdominal or thoracic illness.*	*the day of administration of the contrast agent. IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours.*	*hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours.*	*deciliter 48 hours after administration of the contrast agent* • Number of patients needing RRT
Thiele (2010) n = 249	• Undergoing PCI • Other *patients with ST elevation MI undergoing primary angioplasty with moderate contrast volumes. MI symptoms for under 12 hours, ST segment elevation of at least 0.1mV in at least 2 extremity leads or at least 0.2mV in at least 2 precordial leads*	• IV NAC + IV sodium chloride 0.9% *Pre-contrast: 1200mg IV bd in single bolus Post-contrast: NAC given over 48 hours (4 doses) with 0.9% sodium chloride 1ml/kg/h given for 12 hours.*	• IV sodium chloride 0.9% *Pre-contrast: none Post-contrast: 0.9% sodium chloride 1ml/kg/h given for 12 hours.*	• Contrast induced AKI *sCR ≥25% 72 hours after PCI* • Mortality *At 6 months* • Adverse events *during NAC administration* • Renal failure *need for RRT*
Torigoe (2013) n = 122	• Scheduled for elective coronary arteriography or PIC • Age ≥20 years • eGFR *15-60ml/min/1.73m2*	• IV sodium chloride 0.9% (5 hours) *Pre-procedure: given at a dose of 1ml/kg/hour for 5 hours Post-procedure: given at a dose of 1ml/kg/hour for 24 hours*	• IV sodium chloride (20 hours) *Pre-procedure: given at a dose of 1ml/kg/hour for 20 hours Post-procedure: given at a dose of 1ml/kg/hour for 24 hours*	• Serum creatinine clearance *at 48 hours, maximal absolute and % change in sCr*
Traub (2013) n = 399	• Undergoing CT scan • Age ≥18 years • Other *Undergoing emergency enhanced CT of chest, abdomen,*	• IV NAC + IV sodium chloride 0.9% *Pre-procedure: 200 mg of NAC per hour administered as an infusion of 67 mL per hour of a*	• IV sodium chloride 0.9% *Pre-procedure: 500 mL sodium chloride 0.9%. during 30 min. Post-procedure: IV sodium chloride 0.9%*	• Contrast induced AKI *at 48 to 72 hours, defined as an increase in sCr of at least 44.2 umol/L or 25% over baseline* • Renal failure

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	or pelvis as part of clinical care; 1 or more risk factors for contrast-induced nephropathy (pre-existing renal dysfunction, diabetes, hypertension being treated with antihypertensive medications, CAD, use of nephrotic drugs, liver disease, congestive heart failure, older age (65 years plus), and anemia.)	*solution of 3 g of NAC diluted to a total volume of 1,000 mL with 500 mL sodium chloride 0.9%. during 30 min. Post-procedure: IV sodium chloride 0.9% continuous infusion of 67 mL per hour for at least 2 hours.*	*continuous infusion of 67 mL per hour for at least 2 hours.*	*Moderate renal injury (100% increase in sCr level) or severe renal failure (necessitating RRT), telephone calls were used to identify those with renal injury beyond 72 hours*
Turedi (2016) n = 231	• Undergoing CTPA • Age ≥18 years • CIN *One or more risk factors for CIN* • Other *Undergoing contrast enhanced thoracic CT due to suspected PE, with measurable basal creatinine levels pretomography, measurable serum creatinine levels 48-72 hours posttomography*	• IV NAC + IV sodium chloride 0.9% *Pre-CTPA: 3 mL/kg IV NAC+NS solution (3 g NAC was made up to 1000 mL with NS). Post-CTPA: 1 mL/kg* • IV sodium chloride 0.9% + IV sodium bicarbonate *Pre-CTPA: 3 mL/kg 132 mEq NaHCO3 was made up to 1000 mL with NS Post-CTPA: 1ml/kg for a minimum of 6h*	• IV sodium chloride 0.9% *Pre-CTPA: 3 mL/kg NS alone for 1 hour Post-CTPA: 1 mL/kg IV per hour for a minimum of 6 hour*	• Renal failure *Moderate renal injury (defined as a 100% increase in serum creatinine levels) or severe renal failure developing (requiring hemodialysis or peritoneal dialysis)* • CIN *CIN development measurement of the changes in pre- CTPA basal creatinine levels and post-CTPA creatinine levels measured 48–72 hours following contrast exposure and an increase ≥25% or 0.5 mg/dL in creatinine levels 48–72 hours after contrast exposure compared to basal levels*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
Ueda (2011) n = 60	• Undergoing emergency diagnostic or interventional coronary procedure (such as coronary angiography or PCI)	• IV sodium chloride 0.9% + IV sodium bicarbonate *Pre-procedure: IV sodium chloride 0.9% 0.5 ml/kg as soon as possible after they were admitted, before the administration of contrast. Post-procedure: 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure.*	• IV sodium bicarbonate *Pre-procedure: none Post-procedure: 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure.*	• Contrast induced AKI *at 48 hours, defined as an increase of at least 44.2 umol/L or 25% over baseline sCr.*
Van Mourik (2018) n = 84	• Undergoing CTA • Age ≥18 years • Other *Planned for CTA prior to TAVI* • Chronic kidney disease *3a or above*	• Sodium bicarbonate *pre-procedure: 1.4% 3ml/kg/h given for 1 hour post-procedure: none*	• Sodium chloride 0.9% *re-procedure: 1ml/kg/h for 8 hours post-procedure: 1ml/kg/h for 16 hours*	• Contrast induced AKI *at 2-5 days, defined as increase in creatinine of at least 25% or 44.2umol/L over baseline* • Serum creatinine clearance *% change in sCr between the two hydration protocols at 2-5 days after contrast administration, compared to baesline; absolute change in creatinine.*
Vashegha ni-Farahani (2010) n = 72	• Undergoing angiography • Serum creatinine • Age ≥18 years • Other	• IV sodium bicarbonate _ sodium chloride 0.45% *Pre-procedure: 75 mL of 8.4% sodium bicarbonate to 1 L*	• Sodium chloride 0.45% *Pre-procedure: 1075 mL sodium chloride 0.45% given at 3 ml/kg for 1 hour. Post-procedure: same*	• Contrast induced AKI *at 48 hours and at 5 days, defined as an increase in absolute (at least 44.2 umol/L) or relative (at least*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	candidate for coronary angiography and having at least one of the following: uncontrolled hypertension, compensated severe heart failure (EF <30% or grades III-IV) or a previous pulmonary edema.	*sodium chloride 0.45% given at 3 ml/kg for 1 hour. Post-procedure: same again, given at 1ml/kg for 6 hours.*	*again, given at 1ml/kg for 6 hours.*	*25%) increase over baseline.* • Length of hospital stay • Notes *urine pH was also assessed after initial bolus*
Webb (2004) n = 398	• Undergoing PCI • Age ≥18 years • eGFR *Screening GFR <50ml/min* • Other *Patients with renal dysfunction undergoing cardiac catheterisation or PCI*	• IV NAC + IV sodium chloride 0.9% *Pre-contrast: 200ml 0.9% sodium chloride, plus 500mg (in 50ml of 5% dextrose saline) given over 15 mins within 1 hours of procedure. Post-contrast: 0.9% 1.5ml/kg/hour sodium chloride for 6 hours.*	• IV sodium chloride 0.9% *Pre-contrast: 200ml 0.9% sodium chloride, plus 50ml of 5% dextrose saline (without NAC) given over 15 mins within 1 hours of procedure.Post-contrast: 0.9% 1.5ml/kg/hour sodium chloride for 6 hours.*	• Contrast induced AKI *at 72 hours, defined as reduction in CrCl from baseline of >5ml/min day 2-8, median day 3)* • Mortality *in-hospital mortality* • Renal failure *need for RRT* • Serum creatinine clearance *at 72 hours: increase in serum creatinine of at least 25% or at least 44 umol/L day 2-8 (median day 3)*
Weisbord (2018) n = 5177	• Undergoing angiography: coronary, peripheral, carotid, mesenteric, aortic, renal, and other	• oral NAC + IV sodium chloride 0.9% *oral NAC dose: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days*	• placebo + IV sodium chloride 0.9% *oral placebo dose: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days.*	• CKD progression *confirmed persistent kidney impairment at 90 to 104 days* • Mortality *within 90 days*

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	• eGFR *15 to 44.9 ml per minute per 1.73 m² of body-surface area or 45 to 59.9 ml per minute per 1.73 m² among those with diabetes mellitus* • Received imaging *Patients who were scheduled to undergo coronary or noncoronary angiography* • Other *able and willing to provide informed consent*	*(total oral NAC 2400mg daily for 5 days) IV sodium chloride 0.9% dose: 154 mmol per liter. 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 to 12 ml/kg after angiography* • oral NAC + IV sodium bicarbonate *oral NAC: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days (total oral NAC 2400mg daily for 5 days) IV sodium bicarbonate dose: 1.26% (150 mmol per liter). 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 - 12 ml/kg after angiography.*	*IV sodium chloride 0.9% dose: 154 mmol per liter. 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 to 12 ml/kg after angiography.* • placebo + IV sodium bicarbonate *oral placebo: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days. IV sodium bicarbonate dose: 1.26% (150 mmol per liter). 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 - 12 ml/kg after angiography.*	• Adverse events *hospitalization with acute coronary syndrome, heart failure, or stroke within 90 days. Hospitalization for any cause within 90 days* • CIN *an increase in serum creatinine of either at least 25% or at least 0.5 mg per deciliter (44 µmol per liter) from baseline at 3 to 5 days after angiography* • Need for dialysis *within 90 days* • Composite outcome *death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 to 104 days after angiography and confirmed at subsequent testing within 14 days (defined as persistent impairment in kidney function).*
Wrobel (2010) n = 102	• Undergoing angiography and/or angioplasty	• Sodium chloride 0.9%	• Oral mineral water or boiled water	• Contrast Induced AKI

Short Title	Population	Interventions	Comparator	Outcome measure(s)
	• Diabetes mellitus *undergoing coronary angiography and/or angioplasty* • Other *cardiovascular disease*	*Pre contrast: 6 hours Post-contrast: 12 hours both given at a dose of 1ml/kg/h intravenously*	*Pre contrast: 6-12 hours* *Post-contrast: 12 hours* *both given at a dose of 1ml/kg/h*	*at 48 and 72 hours: defined as an increase in serum creatinine of at least 25% or 44umol/L over baseline* • Renal failure *need for RRT*

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

Network meta-analysis

All analyses are for the outcome CI-AKI as this was the outcome reported by all of the included studies and was the only outcome amenable to NMA. For full GRADE tables see appendix H.

Table 3: Summary GRADE table (outcome: CI-AKI)

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
NAC (IV bolus & oral) + sodium chloride 0.9% (IV) vs no (intravenous) hydration	21,825	RR 0.49 (0.19, 1.24)	Low	Could not differentiate
NAC (IV bolus) + sodium chloride 0.9% (IV) vs no (intravenous) hydration	21,825	RR 0.50 (0.15, 1.64)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.45% (IV) vs no (intravenous) hydration	21,825	RR 0.60 (0.18, 1.75)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.9% (IV) vs no (intravenous) hydration	21,825	RR 0.70 (0.36, 1.39)	Low	Could not differentiate
NAC (oral) vs no (intravenous) hydration	21,825	RR 1.03 (0.27, 3.05)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs no (intravenous) hydration	21,825	RR 0.67 (0.34, 1.33)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs no (intravenous) hydration	21,825	RR 0.59 (0.22, 1.42)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs no (intravenous) hydration	21,825	RR 0.61 (0.36, 1.15)	Low	Could not differentiate
oral fluids vs no (intravenous) hydration	21,825	RR 0.47 (0.15, 1.32)	Low	Could not differentiate
sodium bicarbonate (IV) vs no (intravenous) hydration	21,825	RR 0.59 (0.35, 1.04)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs no (intravenous) hydration	21,825	RR 0.17	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
		(0.00, 1.30)		
sodium chloride 0.45% (IV) vs no (intravenous) hydration	21,825	RR 1.23 (0.57, 2.53)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs no (intravenous) hydration	21,825	RR 1.53 (0.28, 4.92)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs no (intravenous) hydration	21,825	RR 0.74 (0.45, 1.32)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs no (intravenous) hydration	21,825	RR 0.45 (0.20, 1.02)	Low	Could not differentiate
sodium citrate (oral) vs no (intravenous) hydration	21,825	RR 1.13 (0.27, 3.30)	Low	Could not differentiate
NAC (IV bolus) + sodium chloride 0.9% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.04 (0.27, 3.75)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.45% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.24 (0.29, 4.66)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.9% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.44 (0.62, 3.42)	Low	Could not differentiate
NAC (oral) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 2.10 (0.44, 7.94)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.38 (0.57, 3.32)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.20 (0.35, 3.93)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.27 (0.58, 2.93)	Low	Could not differentiate
oral fluids vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 0.96 (0.28, 3.10)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.22 (0.54, 2.79)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 0.34 (0.01, 2.89)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 2.52 (0.85, 7.20)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 3.12 (0.48, 12.49)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
sodium chloride 0.9% (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 1.54 (0.74, 3.37)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 0.93 (0.35, 2.48)	Low	Could not differentiate
sodium citrate (oral) vs NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	21,825	RR 2.31 (0.45, 8.75)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.45% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.20 (0.23, 5.68)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.9% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.38 (0.46, 4.57)	Low	Could not differentiate
NAC (oral) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 2.02 (0.36, 9.73)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.33 (0.43, 4.43)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.16 (0.27, 4.90)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.22 (0.42, 3.97)	Low	Could not differentiate
oral fluids vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 0.93 (0.22, 3.86)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.18 (0.40, 3.74)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 0.33 (0.01, 3.27)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 2.42 (0.66, 9.23)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 2.97 (0.41, 15.08)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 1.48 (0.53, 4.61)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 0.90 (0.27, 3.20)	Low	Could not differentiate
sodium citrate (oral) vs NAC (IV bolus) + sodium chloride 0.9% (IV)	21,825	RR 2.20 (0.37, 10.71)	Low	Could not differentiate
NAC (IV) + sodium chloride 0.9% (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.16 (0.36, 4.35)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
NAC (oral) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.68 (0.46, 5.94)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.11 (0.35, 4.13)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 0.96 (0.40, 2.54)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.02 (0.34, 3.74)	Low	Could not differentiate
oral fluids vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 0.78 (0.18, 3.62)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 0.98 (0.33, 3.50)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 0.27 (0.01, 2.93)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 2.01 (0.96, 4.98)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 2.46 (0.47, 10.53)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.24 (0.42, 4.41)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 0.75 (0.22, 3.02)	Low	Could not differentiate
sodium citrate (oral) vs NAC (IV) + sodium chloride 0.45% (IV)	21,825	RR 1.85 (0.33, 9.33)	Low	Could not differentiate
NAC (oral) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 1.47 (0.35, 4.59)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.96 (0.53, 1.72)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.84 (0.29, 2.24)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.88 (0.56, 1.45)	Low	Could not differentiate
oral fluids vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.67 (0.23, 1.75)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.85 (0.52, 1.39)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.24 (0.01, 1.80)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 1.76 (0.72, 3.96)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 2.20 (0.37, 7.21)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 1.07 (0.73, 1.62)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 0.65 (0.33, 1.24)	Low	Could not differentiate
sodium citrate (oral) vs NAC (IV) + sodium chloride 0.9% (IV)	21,825	RR 1.62 (0.36, 5.06)	Low	Could not differentiate
NAC (oral) + sodium bicarbonate (IV) vs NAC (oral)	21,825	RR 0.65 (0.21, 2.75)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (oral)	21,825	RR 0.57 (0.25, 1.50)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (oral)	21,825	RR 0.60 (0.20, 2.48)	Low	Could not differentiate
oral fluids vs NAC (oral)	21,825	RR 0.46 (0.11, 2.32)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (oral)	21,825	RR 0.58 (0.19, 2.33)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (oral)	21,825	RR 0.16 (0.00, 1.83)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (oral)	21,825	RR 1.19 (0.51, 3.51)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (oral)	21,825	RR 1.47 (0.26, 6.92)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (oral)	21,825	RR 0.73 (0.25, 2.94)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (oral)	21,825	RR 0.44 (0.13, 1.97)	Low	Could not differentiate
sodium citrate (oral) vs NAC (oral)	21,825	RR 1.09 (0.19, 5.98)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.45% (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.87 (0.30, 2.39)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.92 (0.62, 1.44)	Low	Could not differentiate
oral fluids vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.70 (0.24, 1.87)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.88 (0.56, 1.43)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.25 (0.01, 1.88)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 1.83 (0.75, 4.20)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 2.29 (0.39, 7.46)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 1.11 (0.73, 1.79)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 0.68 (0.32, 1.43)	Low	Could not differentiate
sodium citrate (oral) vs NAC (oral) + sodium bicarbonate (IV)	21,825	RR 1.69 (0.38, 5.24)	Low	Could not differentiate
NAC (oral) + sodium chloride 0.9% (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 1.06 (0.42, 3.00)	Low	Could not differentiate
oral fluids vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 0.80 (0.21, 3.03)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 1.02 (0.40, 2.80)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 0.28 (0.01, 2.63)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 2.09 (1.37, 3.37)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 2.56 (0.55, 8.71)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 1.28 (0.52, 3.49)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 0.78 (0.26, 2.47)	Low	Could not differentiate
sodium citrate (oral) vs NAC (oral) + sodium chloride 0.45% (IV)	21,825	RR 1.91 (0.37, 7.83)	Low	Could not differentiate
oral fluids vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 0.76 (0.27, 1.89)	Low	Could not differentiate
sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 0.96 (0.65, 1.37)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 0.27 (0.01, 1.97)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 2.00 (0.85, 4.11)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 2.50 (0.43, 7.46)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 1.21 (0.91, 1.61)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 0.74 (0.36, 1.40)	Low	Could not differentiate
sodium citrate (oral) vs NAC (oral) + sodium chloride 0.9% (IV)	21,825	RR 1.84 (0.42, 5.30)	Low	Could not differentiate
sodium bicarbonate (IV) vs oral fluids	21,825	RR 1.26 (0.51, 3.47)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs oral fluids	21,825	RR 0.36 (0.01, 2.98)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs oral fluids	21,825	RR 2.61 (0.81, 8.87)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs oral fluids	21,825	RR 3.23 (0.47, 14.98)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs oral fluids	21,825	RR 1.59 (0.67, 4.28)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs oral fluids	21,825	RR 0.97 (0.33, 3.05)	Low	Could not differentiate
sodium citrate (oral) vs oral fluids	21,825	RR 2.39 (0.44, 10.47)	Low	Could not differentiate
sodium bicarbonate (oral) + oral fluids vs sodium bicarbonate (IV)	21,825	RR 0.28 (0.01, 2.04)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs sodium bicarbonate (IV)	21,825	RR 2.08 (0.92, 4.36)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (IV)	21,825	RR 2.59 (0.45, 8.03)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs sodium bicarbonate (IV)	21,825	RR 1.26 (0.95, 1.73)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (IV)	21,825	RR 0.77 (0.39, 1.46)	Low	Could not differentiate
sodium citrate (oral) vs sodium bicarbonate (IV)	21,825	RR 1.91 (0.45, 5.54)	Low	Could not differentiate
sodium chloride 0.45% (IV) vs sodium bicarbonate (oral) + oral fluids	21,825	RR 7.37 (0.88, 245.40)	Low	Could not differentiate
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (oral) + oral fluids	21,825	RR 8.98 (0.67, 339.30)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs sodium bicarbonate (oral) + oral fluids	21,825	RR 4.43 (0.63, 145.70)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (oral) + oral fluids	21,825	RR 2.71 (0.34, 91.26)	Low	Could not differentiate
sodium citrate (oral) vs sodium bicarbonate (oral) + oral fluids	21,825	RR 6.70 (0.58, 252.60)	Low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
sodium chloride 0.45% (IV) + sodium bicarbonate (IV) vs sodium chloride 0.45% (IV)	21,825	RR 1.24 (0.27, 3.58)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs sodium chloride 0.45% (IV)	21,825	RR 0.61 (0.30, 1.36)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium chloride 0.45% (IV)	21,825	RR 0.37 (0.14, 0.99)	Low	May favour sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
sodium citrate (oral) vs sodium chloride 0.45% (IV)	21,825	RR 0.92 (0.19, 3.23)	Low	Could not differentiate
sodium chloride 0.9% (IV) vs sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	21,825	RR 0.48 (0.16, 2.78)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	21,825	RR 0.30 (0.08, 1.86)	Low	Could not differentiate
sodium citrate (oral) vs sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	21,825	RR 0.74 (0.12, 5.36)	Low	Could not differentiate
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium chloride 0.9% (IV)	21,825	RR 0.61 (0.32, 1.09)	Low	Could not differentiate
sodium citrate (oral) vs sodium chloride 0.9% (IV)	21,825	RR 1.52 (0.35, 4.36)	Low	Could not differentiate
sodium citrate (oral) vs sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	21,825	RR 2.48 (0.52, 8.63)	Low	Could not differentiate

(a) Could not differentiate: crosses line of no effect; May favour: confidence intervals do not cross line of no effect but cross MID; Favours: confidence intervals do not cross line of no effect or MID

Pairwise meta-analysis

All analyses are for the outcome CI-AKI as this was the outcome reported by all of the included studies. For full GRADE tables see appendix H.

Table 4: Summary GRADE table (outcome: CI-AKI)

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.45% vs no (intravenous) hydration[b]	660[c]	RR 0.96 (0.54 to 1.68)	Very low	Could not differentiate
Sodium chloride 0.9% vs no (intravenous) hydration	903	RR 0.86 (0.6 to 1.24)	Low	Could not differentiate
Sodium chloride 0.9% vs oral fluids	376	RR 1.52 (0.72 to 3.2)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45%[b]	1,383	RR 0.36 (0.13 to 1.0)	Very low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% vs sodium bicarbonate	5,412	RR 1.04 (0.88 to 1.23)	Moderate	Could not differentiate
Sodium chloride 0.9% vs oral sodium bicarbonate + oral fluids[b]	48	RR 4.67 (0.61 to 35.84)	Very low	Could not differentiate
Sodium chloride 0.9% (5 hours) vs sodium chloride 0.9% (20 hours)[b]	122	RR 1.03 (0.15 to 7.1)	Very low	Could not differentiate
Sodium chloride 0.45% + sodium bicarbonate vs sodium chloride 0.45%[b]	72	RR 1.25 (0.37 to 4.28)	Very low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9%	542	RR 0.46 (0.19 to 1.11)	Very low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate[b]	59	RR 4.14 (0.96 to 17.87)	Low	Could not differentiate
Oral sodium bicarbonate + oral fluids vs oral fluids[c]	43	RR 1.05 (0.07 to 15.69)	Very low	Could not differentiate
Sodium bicarbonate vs no (intravenous) hydration	522	RR 0.51 (0.33 to 0.78)	Moderate	Favours sodium bicarbonate
Sodium bicarbonate vs oral fluids[b]	43	RR 2.1 (0.2 to 21.42)	Very low	Could not differentiate
Sodium bicarbonate vs oral sodium citrate[b]	86	RR 0.6 (0.15 to 2.36)	Very low	Could not differentiate
Sodium bicarbonate vs oral sodium bicarbonate + oral fluids[b]	42	RR 2.0 (0.2 to 20.41)	Very low	Could not differentiate
Oral sodium citrate vs no (intravenous) hydration[b]	87	RR 1.28 (0.37 to 4.45)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%	1,154	RR 0.50 (0.37 to 0.70)	Very low	Favours oral NAC + sodium chloride 0.45%
Oral NAC + sodium chloride 0.45% vs oral NAC[b]	376[c]	RR 0.62 (0.45 to 0.88)	Very low	May favour oral NAC + sodium chloride 0.45%
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%	6,597	RR 0.96 (0.83 to 1.10)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium bicarbonate	3,059	RR 0.89 (0.71 to 1.12)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate	4,056	RR 0.81 (0.67 to 0.98)	Low	May favour oral NAC + sodium chloride 0.9%
Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9%[b]	204	RR 1.08 (0.53 to 2.18)	Very low	Could not differentiate

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Oral NAC + sodium bicarbonate vs sodium chloride 0.9%	2,661	RR 1.15 (0.91 to 1.45)	Moderate	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium bicarbonate	3,130	RR 1.08 (0.86 to 1.34)	Moderate	Could not differentiate
IV NAC + sodium chloride 0.45% vs sodium chloride 0.45%	384	RR 0.46 (0.16 to 1.36)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%	1,915	RR 1.05 (0.84 to 1.32)	Low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate	242	RR 1.23 (0.74 to 2.03)	Low	Could not differentiate
IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%	559	RR 0.61 (0.21 to 1.83)	Very low	Could not differentiate
IV NAC (bolus) + sodium chloride 0.9% vs sodium chloride 0.9%[b]	249	RR 0.70 (0.40 to 1.22)	Moderate	Could not differentiate

(a) Could not differentiate: crosses line of no effect; May favour: confidence intervals do not cross line of no effect but cross MID; Favours: confidence intervals do not cross line of no effect or MID
(b) Comparison reported by a single RCT
(c) In participants with serum creatinine <132.6µmol/l
(d) In participants with serum creatinine ≥132.6µmol/l
(e)

Table 5: Summary GRADE table; Pre-specified subgroups on pairwise data (outcome: CI-AKI)

Comparison (subgroup)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% vs no (intravenous) hydration (diabetes)[b]	65	RR 1.21 (0.6 to 2.44)	Very low	Could not differentiate
Sodium chloride 0.9% vs no (intravenous) hydration (older people >75 years)[b]	65	RR 1.10 (0.6 to 2.01)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (chronic kidney disease)[b]	286	RR 0.54 (0.14 to 2.10)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (diabetes)[b]	217	RR 0.08 (0.0 to 1.39)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (low volume of contrast agent)[b]	864	RR 0.83 (0.25 to 2.69)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (high volume of contrast agent)[b]	519	RR 0.06 (0.0 to 1.08)	Very low	Could not differentiate
Sodium bicarbonate vs no (intravenous) hydration (diabetes)[b]	65	RR 0.55 (0.21 to 1.43)	Very low	Could not differentiate
Sodium bicarbonate vs no (intravenous) hydration (older people >75 years)[b]	67	RR 0.56 (0.26 to 1.2)	Low	Could not differentiate

Comparison (subgroup)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (chronic kidney disease)[b]	19	RR 1.03 (0.35 to 3.05)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (diabetes)	122	RR 1.5 (0.7 to 3.24)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (chronic kidney disease)[b]	367	RR 1.14 (0.51 to 2.58)	Low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (diabetes)	1,566	RR 0.95 (0.75 to 1.21)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (older people >75 years)[b]	18	RR 0.79 (0.38 to 1.64)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (low volume of contrast agent)[b]	18	RR 1.18 (0.74 to 1.89)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (high volume of contrast agent)	125	RR 0.98 (0.35 to 2.72)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (diabetes)[b]	121	RR 1.58 (0.69 to 3.58)	Low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (low volume of contrast agent)[b]	271	RR 0.24 (0.05 to 1.13)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (high volume of contrast agent)	266	RR 1.11 (0.59 to 2.09)	Low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (chronic kidney disease)[b]	98	RR 0.72 (0.25 to 2.07)	Low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (diabetes)[b]	160	RR 0.67 (0.11 to 3.88)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (older people >75 years)[b]	160	RR 0.08 (0 to 1.34)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (high volume of contrast agent)	187	RR 0.5 (0.08 to 3.18)	Very low	Could not differentiate

(a) Could not differentiate: crosses line of no effect; May favour: confidence intervals do not cross line of no effect but cross MID; Favours: confidence intervals do not cross line of no effect or MID
(b) Comparison reported by a single RCT

Table 6: Summary GRADE table; Other outcomes

Comparison (outcome)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% vs no (intravenous) hydration (in-hospital mortality)[b]	300	RR 0.62 (0.21 to 1.87)	Very low	Could not differentiate

Comparison (outcome)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% vs no (intravenous) hydration (all-cause mortality)[b]	660	RR 0.14 (0.01 to 2.79)	Low	Could not differentiate
Sodium chloride 0.9% vs no (intravenous) hydration (need for renal replacement therapy: dialysis)	4,909	RR 1.04 (0.62 to 1.75)	Low	Could not differentiate
Sodium chloride 0.9% vs no (intravenous) hydration (adverse events)	960	RR 4.59 (0.16 to 134.39)	Very low	Could not differentiate
Sodium chloride 0.9% vs oral fluids (all-cause mortality)[b]	225	RR 3.19 (0.13 to 77.5)	Very low	Could not differentiate
Sodium chloride 0.9% vs oral fluids (need for renal replacement therapy: dialysis)[b]	225	RR 3.19 (0.13 to 77.5)	Very low	Could not differentiate
Sodium chloride 0.9% vs oral fluids (length of hospital stay in days)[b]	49	MD -0.38 (-3.81 to 3.05)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (mortality)[b]	530	RR 0.33 (0.03 to 3.18)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (need for renal replacement therapy: dialysis)[b]	1,383	RR 1.02 (0.06 to 16.26)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium chloride 0.45% (adverse events)[b]	530	RR 0.82 (0.41 to 1.64)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (all-cause mortality [30 days])[b]	353	RR 0.98 (0.2 to 4.8)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (all-cause mortality [>30 days])	3,242	RR 1.36 (0.65 to 2.83)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (in-hospital mortality)	359	RR 2.05 (0.57 to 7.35)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (need for renal replacement therapy)	3,301	RR 0.93 (0.54 to 1.61)	Low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (adverse events)	773	RR 1.74 (0.94 to 3.21)	Low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (adverse events: heart failure)	845	RR 1.80 (0.59 to 5.48)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate (length of hospital stay in days)	174	MD -0.06 (-2.3 to 2.18)	Very low	Could not differentiate
Sodium chloride 0.9% vs oral sodium bicarbonate + oral fluids (length of hospital stay in days)[b]	48	MD -2.72 (-7.25 to 1.81)	Very low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9% (in-hospital mortality)[b]	172	RR 0.85 (0.39 to 1.87)	Low	Could not differentiate

Comparison (outcome)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9% (need for renal replacement therapy)	387	RR 0.72 (0.36 to 1.44)	Low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9% (adverse events)[b]	144	RR 0.33 (0.01 to 8.05)	Low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate (in-hospital mortality)[b]	59	RR 0.69 (0.12 to 3.83)	Very low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate (adverse events)[b]	59	RR 1.15 (0.55 to 2.41)	Very low	Could not differentiate
Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate (length of hospital stay in days)[b]	60	MD -1.40 (-10.90 to 8.10)	Very low	Could not differentiate
Sodium bicarbonate vs oral fluids (length of hospital stay in days)[b]	43	MD -0.27 (-3.48 to 2.94)	Very low	Could not differentiate
Sodium bicarbonate vs oral sodium bicarbonate + oral fluids (length of hospital stay in days)[b]	48	MD -2.81 (-7.10 to 1.48)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (long-term mortality)[b]	180	RR 1.19 (0.27 to 5.18)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (in-hospital mortality)[b]	180	RR 0.18 (0.01 to 3.68)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (need for renal replacement therapy: dialysis)	484	RR 0.69 (0.13 to 3.52)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (adverse events)	636	RR 1.61 (1.01 to 2.56)	Very low	May favour sodium chloride 0.45%
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (length of hospital stay in days)	116	MD -1.24 (-3.94 to 1.45)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% (readmission for AKI)[b]	180	RR 0.89 (0.44 to 1.82)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (all-cause mortality [30 days])[b]	205	RR 0.14 (0.01 to 2.76)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (all-cause mortality [30 days - 1 year])	2,687	RR 1.38 (0.9 to 2.12)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (in-hospital mortality)[b]	156	RR 2.56 (0.51 to 12.83)	Very low	Could not differentiate

Comparison (outcome)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (need for renal replacement therapy: dialysis)	5,500	RR 0.83 (0.48 to 1.46)	Low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (adverse events)	4,907	RR 0.94 (0.73 to 1.22)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (hospital length of stay in days)[b]	200	MD -0.50 (-0.93 to -0.07)	High	Favours oral NAC + sodium chloride 0.9% (estimated MID 1.0)[c]
Oral NAC + sodium chloride 0.9% vs sodium bicarbonate (all-cause mortality [30 days])[b]	310	RR 3.08 (0.13 to 74.98)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium bicarbonate (all-cause mortality [90 days])[b]	2,492	RR 1.23 (0.78 to 1.93)	Low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs sodium bicarbonate (need for renal replacement therapy: dialysis)[b]	2,492	RR 0.89 (0.43 to 1.81)	Low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (all-cause mortality [30 days])	691	RR 0.44 (0.06 to 2.94)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (all-cause mortality [30 days-6 months])	3,379	RR 1.27 (0.82 to 1.95)	Moderate	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate (need for renal replacement therapy: dialysis)[b]	2,495	RR 0.89 (0.44 to 1.81)	Low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9% (all-cause mortality [30 days])[b]	204	RR 0.33 (0.01 to 8.09)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9% (all-cause mortality [1 year])[b]	204	RR 0.67 (0.28 to 1.56)	Very low	Could not differentiate
Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9% (need for renal replacement therapy: dialysis)[b]	204	RR 3.0 (0.12 to 72.79)	Very low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium chloride 0.9% (all-cause mortality [90 days])[b]	2,501	RR 0.95 (0.57 to 1.61)	Low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium chloride 0.9% (need for renal replacement therapy: dialysis)[b]	2,501	RR 1.06 (0.52 to 2.13)	Low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium bicarbonate (all-cause mortality [30 days])[b]	313	RR 5.03 (0.24 to 103.97)	Very low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium bicarbonate (all-cause mortality [90 days])[b]	2,511	RR 0.82 (0.49 to 1.35)	Low	Could not differentiate

Comparison (outcome)	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Oral NAC + sodium bicarbonate vs sodium bicarbonate (need for renal replacement therapy: dialysis)[b]	2,511	RR 1.0 (0.5 to 1.99)	Low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium bicarbonate (adverse events)[b]	60	RR 3.41 (0.14 to 80.59)	Very low	Could not differentiate
IV NAC + sodium chloride 0.45% vs sodium chloride 0.45% (all-cause mortality [1 year])[b]	81	RR 0.72 (0.28 to 1.83)	Very low	Could not differentiate
IV NAC + sodium chloride 0.45% vs sodium chloride 0.45% (in-hospital mortality)	297	RR 0.61 (0.25 to 1.5)	Very low	Could not differentiate
IV NAC + sodium chloride 0.45% vs sodium chloride 0.45% (need for renal replacement therapy: dialysis)[b]	81	RR 0.36 (0.02 to 8.54)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (all-cause mortality [up to 8 days])[b]	447	RR 1.44 (0.47 to 4.48)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (all-cause mortality [up to 30 days])	1,050	RR 0.69 (0.27 to 1.81)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (all-cause mortality [1 year])[b]	205	RR 1.73 (0.71 to 4.22)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (in-hospital mortality)	570	RR 0.94 (0.45 to 1.96)	Low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (need for renal replacement therapy)	448	RR 0.68 (0.34 to 1.36)	Very low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% (length of hospital stay in days)[b]	398	MD -0.40 (-0.98 to 0.18)	Moderate	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate (in-hospital mortality)[b]	170	RR 1.10 (0.49 to 2.45)	Low	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate (need for renal replacement therapy)	242	RR 1.00 (0.45 to 2.22)	Low	Could not differentiate
IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (in-hospital mortality)[b]	352	RR 0.31 (0.13 to 0.74)	Moderate	Favours IV NAC bolus + oral NAC + sodium chloride 0.9%
IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% (need for renal replacement therapy)[b]	308	RR 0.31 (0.08 to 1.23)	Low	Could not differentiate

(a) Could not differentiate: crosses line of no effect; May favour: confidence intervals do not cross line of no effect but cross MID; Favours: confidence intervals do not cross line of no effect or MID

(b) Comparison reported by a single RCT

(c) MID calculated using the SD of the control group

Table 7: Summary GRADE table; Sensitivity analysis on pairwise data excluding studies with a high risk of bias (outcome: CI-AKI)

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect[a]
Sodium chloride 0.9% vs oral fluids	274	RR 1.54 (0.68 to 3.51)	Very low	Could not differentiate
Sodium chloride 0.9% vs sodium bicarbonate	5,353	RR 1.01 (0.85 to 1.19)	High	Could not differentiate
Sodium bicarbonate vs no (intravenous) hydration	435	RR 0.48 (0.31 to 0.77)	Moderate	Favours sodium bicarbonate
Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%	911	RR 0.61 (0.42 to 0.88)	Very low	May favour oral NAC + sodium chloride 0.45%
Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%	6,228	RR 0.99 (0.85 to 1.14)	High	Could not differentiate
Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate	3,752	RR 0.83 (0.67 to 1.01)	Low	Could not differentiate
Oral NAC + sodium bicarbonate vs sodium bicarbonate	2,770	RR 1.12 (0.89 to 1.42)	Moderate	Could not differentiate
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%	1,517	RR 1.02 (0.78 to 1.33)	Very low	Could not differentiate
IV NAC bolus + oral NAC + IV sodium chloride 0.9% vs IV sodium chloride 0.9%	352	RR 0.35 (0.23 to 0.55)	Moderate	Favours IV NAC bolus + oral NAC + IV sodium chloride 0.9%

(d) Could not differentiate: crosses line of no effect; May favour: confidence intervals do not cross line of no effect but cross MID; Favours: confidence intervals do not cross line of no effect or MID

See appendix H for full GRADE tables.

Economic evidence

A search was conducted to identify economic evaluations relevant to the review question (see Appendix C – Literature search strategies). Search sets covering the original interventions were date limited from January 2013 (when the original search was conducted), while an additional search set covered an expanded version of the fluid therapy terms and was not date limited. The search returned a total of 135 records, 131 of which were excluded on the basis of title and abstract. The remaining 4 studies were fully inspected and none were included in the synthesis. No additional studies were identified during inspection of the full publications and reference lists. The economic evidence study selection is presented as a PRISMA diagram in Appendix I – Economic evidence study selection.

Included studies

No studies were included.

Excluded studies

Details of excluded studies are provided in Appendix M – Excluded studies.

Summary of studies included in the economic evidence review

No economic evaluations relevant to the review question were found.

Economic model

An economic model was developed to answer the review question 'What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?'. Table 8 presents an economic evidence profile summarising the model. See Appendix L – Health economic analysis for a full model report (including a list of interventions and comparators).

Table 8: Original cost–utility model – economic evidence profile

Limitations	Applicability	Other comments	Summary of cost-effectiveness results[a]		Uncertaity
Minor limitations	Directly applicable	Markov decision-analytic model with a lifetime time horizon	Base case	Sodium bicarbonate (oral) + oral fluids dominates all other options	Cost-effectiveness conclusion sensitive to relative effect of sodium bicarbonate (oral) + oral fluids versus no intervention.
			Without sodium bicarbonate (oral) + oral fluids[b]	ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids: £510,922 All other interventions dominated	Cost-effectiveness conclusion sensitive to the relative treatment effects for oral fluids alone, or sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus no intervention. PSA indicates that oral fluids are likely to be the most cost-effective intervention when QALYs valued at £20,000.
			Without sodium bicarbonate (oral) + oral fluids, emergency population[c]	ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids: £16,112 All other interventions dominated	Multiple parameters have the potential to alter the cost-effectiveness conclusion. When comparing sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids, altering relative treatment effects has the largest effect on results; however, other parameters that make very little difference to results in absolute terms still have the potential to change the cost-effectiveness conclusion at a threshold of £20,000/QALY. PSA indicates that regimens containing sodium chloride 0.9% and/or sodium bicarbonate have the highest probability of cost effectiveness when QALYs are valued at ~£15,000 or more.
			Without sodium bicarbonate (oral) + oral fluids, elective population[d]	ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids: £655,323 All other interventions dominated	Cost-effectiveness conclusion sensitive to the relative treatment effects for oral fluids alone, or sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus no intervention. PSA indicates that oral fluids are likely to be the most cost-effective intervention when QALYs valued at £20,000.

ICER, incremental cost-effectiveness ratio; IV, intravenous; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.

(a) For full incremental cost–utility results, please see Appendix L – Health economic analysis.

(b) Removed from the decision space as the committee was not convinced that the evidence for sodium bicarbonate (oral) + oral fluids is sufficiently robust for it to be recommended.

(c) Uses pooled baseline risk of CI-AKI from 0.9% sodium chloride arms of emergency trials and assumes an inpatient population (no excess bed day costs).

(d) Uses pooled baseline risk of CI-AKI from 0.9% sodium chloride arms of elective trials.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the key outcome for people at risk of contrast induced acute kidney injury (CI-AKI) was the occurrence of CI-AKI. Committee members highlighted that CI-AKI was normally diagnosed within 24-48 hours after the contrast was given, but had to be diagnosed within 7 days of contrast being given (this was to allow for delays in testing) because later acute kidney injury (AKI) diagnosis was not likely to be related to the use of iodine based contrast media. The committee agreed that chronic kidney disease (CKD) progression, mortality, needing renal replacement therapy, and adverse events (including heart failure) were also important outcomes as these could indicate that an intervention was not working or might be harmful. However, these outcomes were not prioritised because the committee expected that there would be a shortage of evidence, making it harder to use them for decision making.

The quality of the evidence

Overall, the quality of the pairwise evidence varied from high to very low, with the main reasons for downgrading being due to imprecision of the evidence on the relative effectiveness of different fluids at preventing CI-AKI and risk of bias of included studies. In most of the pairwise comparisons, imprecision was considered to be serious (95% confidence interval crossing one end of the defined (minimal clinically important difference) MID interval [0.8, 1.25]) or very serious (95% confidence interval crossing both ends of the defined MID interval [0.8, 1.25]). Risk of bias for some of the included studies was due to lack of detailed report of the randomisation process, lack of report that protocols were pre-registered, and either participants were aware of which intervention were assigned or the assignment of interventions was not well described.

The quality of the evidence was low for the network meta analysis (NMA). The main reasons for downgrading were due to risk of bias of the included studies for the reasons mentioned above.

As a result of most of the evidence being of very low to moderate quality the committee did not feel able to make strong recommendations and instead made 'consider' recommendations.

CI-AKI was reported using different definitions (see appendix P for a list of reported CI-AKI definitions). The committee agreed to prioritise definitions for data extraction based on their clinical usefulness (see appendix Q for the prioritisation of CI-AKI definitions). CI-AKI events were reported at different time points ranging from 1 to 5 days. The committee agreed that randomised controlled trials (RCTs) reporting different time points could be analysed together as long as the longest time point was 5 days or less. The committee also agreed that RCTs could be analysed together grouping different regimes, durations, and volumes/dosage within a type of fluid.

The committee highlighted that high-osmolar contrast agents are currently not recommended due to the high risk of adverse reactions. Therefore, it made sure that all included studies used contrast agents that were either low-osmolar or iso-osmolar. There was one study (Solomon 2015) stating that the choice of contrast agent was left to individual participants

sites, so the committee were unable to be sure that none of the sites used high osmolar contrast agent.

The committee noted that all included studies reported data on occurrence of CI-AKI, but there was limited evidence for the rest of outcomes (CKD progression, mortality, need for renal replacement therapy, adverse events, hospital stay, readmission for AKI, and health related quality of life). There was also limited evidence on subgroup analyses. The committee noted that none of the subgroup analyses showed evidence of an effect from any of the interventions on the incidence of CI-AKI. Regarding the rest of the outcomes, there was evidence of fewer adverse events with sodium chloride 0.45% compared to oral NAC + sodium chloride 0.45% but the confidence interval crossed the MID; fewer days in hospital with NAC + sodium chloride 0.9% compared to sodium chloride 0.9%; and fewer deaths in-hospital with IV NAC bolus + oral NAC + sodium chloride 0.9% compared to sodium chloride 0.9%. This evidence came from single RCTs and was not compelling compared to the much greater statistical power of the NMA, therefore the committee agreed to make decisions based on the NMA findings.

Sensitivity analyses for the pairwise data did not alter the interpretation of the effects of the treatments with 2 exceptions that were not considered sufficient to warrant running NMA sensitivity analyses for the CI-AKI outcome:

- Oral N-acetylcysteine (NAC) + sodium chloride 0.45% compared to sodium chloride 0.45%. Sensitivity analysis showed that oral NAC + sodium chloride 0.45% could not demonstrate a meaningful difference when studies at high risk of bias were removed (previously, a meaningful effect exceeding the MID [0.8, 1.25]).
- Oral NAC + sodium chloride 0.9% compared to oral NAC + sodium bicarbonate. Sensitivity analysis showed that oral NAC + sodium chloride 0.9% could not differentiate to oral NAC + sodium bicarbonate when studies at high risk of bias were removed (previously, could not demonstrate a meaningful difference crossing one end of the MID [0.8, 1.25]).

NMA analyses and NMA model inconsistency checks

The NMA model included 17 different interventions. The results of this model showed substantial within-contrast heterogeneity. Therefore, a number of study-level characteristics were explored but no intervention-level differences could explain the heterogeneity. As a next step, other NMA models were built and explored to look for a parsimonious model and to improve clinical interpretability. These models broke down each intervention into its constituent elements:

- underlying fluid
  - sodium chloride 0.9% (intravenous [IV])
  - no (intravenous) hydration
  - sodium bicarbonate (IV)
  - sodium chloride 0.45% (IV)
  - sodium citrate (oral)
  - oral fluids
  - sodium bicarbonate (oral) + oral fluids
  - sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
  - sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
- whether NAC was given or not (oral or intravenous)

- what fluid was given at pre- and post- procedure using iodinated contrast
- type of procedure was done
  - intervention
  - diagnostic
  - both
- setting
  - elective
  - emergency
  - both

All of the different NMA models that were run had similar heterogeneity and total residual deviance. Therefore the simpler 17 intervention model was reverted to because it made fewer assumptions and had marginally lower heterogeneity compared with the rest of the models.

NMA model inconsistency checks were carried out to assess the consistency assumption in the NMA models used to estimate the comparative clinical and cost effectiveness of NAC and/or fluids in preventing CI-AKI in at risk adults.

Firstly, parts of the network containing the potentially inconsistent studies were identified. The characteristics of the studies identified as being potentially inconsistent were examined in detail to determine if there were any differences between these studies and the other studies in the loop in question that could explain the inconsistency. If substantial differences were identified this might suggest that the potentially inconsistent studies should be excluded from the NMA or placed in a separate/different node in the network. These checks focused on key factors that the committee had previously mentioned during their discussions that could potentially alter the results substantially, such as type of procedure (intervention versus diagnostic) and setting (elective or emergency).

Secondly, the characteristics of the other RCTs within the loops were examined to determine whether any of them could be causing the inconsistency instead. In both cases, no differences in study characteristics were identified that could account for the inconsistency and therefore there were no reasons to exclude any of the individual studies.

Thirdly, the NMA model was re-run without the potentially inconsistent study (Ueda 2011) to investigate the effect this study had on the NMA results. This analysis showed minor differences in results compared to the original NMA which included Ueda 2011.

Finally, the NMA model including 17 different interventions and the inconsistency checks were used to interpret the results related to the occurrence of CI-AKI. These results were used by the committee in conjunction with the outcomes of the health economic model when it discussed the benefits and harms of the different interventions in preventing CI-AKI in at risk adults (see next section which includes the discussion of the committee).

This information allowed the committee to discuss the relative effectiveness of all of the combinations of NAC and fluids compared to each other and therefore it was able to be clearer about their recommendations even though the quality of the evidence ws not sufficient to make strong recommendations.

Benefits and harms

Occurrence of CI-AKI was similar across interventions (either oral or intravenous fluids) in the NMA and there was limited evidence for other outcomes and subgroup analyses from the pairwise data.

The committee agreed that outpatients are generally at lower risk of CI-AKI compared with inpatients with particular risk factors (acutely ill, estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2, renal transplant, increased volume of contrast agent, intra-arterial administration of contrast agent) so it made separate recommendations for each group of patients. Most of the risk factors given above were taken from recommendation 1.1.6 of the current guideline apart from the level of eGFR which was based on the committee's clinical knowledge and experience. The committee agreed that a level of eGFR < 30 ml/min/1.73 m^2 was appropriate.The committee noted that the evidence was unclear about the effectiveness of intravenous/oral fluids stratified by different eGFR subgroups on the incidence of CI-AKI. It made a research recommendation to investigate whether the risk of CI-AKI can be stratified by eGFR.. It noted that it might not be possible to do this research on people with very low eGFRs because they may be too high risk to be included in research studies. However it agreed that better evidence of risk stratification for CI-AKI in people with higher eGFRs would still improve clinical practice and patient safety. The committee also agreed that, based on their experience and expertise, the risk for intra-arterial administration depends on the site of the injection, and is particularly high with first-pass renal exposure, because the contrast medium passes into the kidneys relatively undiluted. The committee agreed to be more specific about what constituted a 'large volume' of contrast agent, and while it agreed that there is no simple definition for this, a useful heuristic is to consider doses higher than a standard diagnostic dose as a 'large volume'

The committee noted the evidence showed oral fluids were not worse than intravenous fluids for preventing CI-AKI and, on that basis, it agreed that it did not seem necessary to bring outpatients into hospital to give them intravenous fluids prior to receiving iodine based contrast media. Therefore, the committee recommended the use of oral hydration in these patients. The committee highlighted the importance of adequate hydration in people having intravenous iodine based contrast media. The committee discussed the different regimens used in the included studies, but decided that it should not recommend a specific regimen as this would need to be adapted to people's situations (for example, people with heart failure, age [some frail older people might be less likely to be able to follow an oral fluids regimen if the volume of fluid is high], other conditions [people might have gastric problems preventing them to drink the full amount of oral fluids]) and preferences (some people might prefer to drink tea or coffee as well as water). The different oral regimens seen in the evidence presented to the committee were:

- patients were encouraged to drink as much spring or tap water as possible 12 hours before and 12 hours after the procedure (Akyuz 2014)
- 500 mL of water 4 h prior to contrast exposure stopping 2 h prior to procedure and 600 mL of water post procedure (Cho 2010)
- oral mineral water or boiled water (1ml/kg/h) 6 to 12 hours before the procedure and 12 hours after the procedure (Wrobel 2010)

Similarly, the committee agreed that many inpatients could be encouraged to hydrate orally before and after being given a contrast agent, however, the committee agreed that inpatients at particularly high risk should receive intravenous fluids for volume expansion when having a contrast agent. It noted the importance of maintaining the correct fluid balance in these patients because fluids (oral or intravenous) might be harmful for some people leading to

fluid overload and cardiovascular events. The evidence from the NMA showed that sodium chloride 0.9% and sodium bicarbonate appear to be equivalent for preventing CI-AKI. Therefore the committee recommended the use of intravenous volume expansion for these patients and kept the recommended interventions from the previous guideline: isotonic sodium bicarbonate or sodium chloride 0.9%.

The committee also highlighted the importance of adequate hydration in all inpatients having iodine based contrast media by having their hydration level assessed, and that safety was particulary important with inpatients at high risk of CI-AKI. The committee discussed some of the contraindications for volume expansion (for example, hypervolemic hyponatremia or active decompensated heart failure [these were some of the exclusion criteria listed in Akyuz 2014]) but it did not make a recommendation about this because it agreed that clinical judgment was the key factor in these cases.

The committee also noted that the NMA did not show evidence for the use of NAC either oral or intravenous and that NAC is not routinely used in clinical practice. Therefore, this intervention was not recommended, however due to the poor quality of the evidence, the committee did not feel able to make a ‘do not offer’ recommendation for NAC and recommended it be included in future research. The rank probability histogram for sodium bicarbonate (oral) + oral fluids showed that this treatment had a probability of around 65% of being the best treatment but histograms were associated with a high degree of uncertainty.

The committee highlighted that it was crucial that imaging should not be delayed purely for volume expansion and it asked for this to be made clearer in editorial refresh of recommendation 1.1.6 which includes a list of risk factors for CI-AKI. The last sentence in that recommendation (‘Ensure that risk assessment does not delay emergency imaging’) has been brought to the start of the recommendation (see full guideline recommendation 1.1.6).

The committee clarified that renal transplant patients were excluded from the evidence of this review but they are mentioned in the updated recommendation as a group at high risk of CI-AKI.

The committee agreed that it was important to discuss with a nephrology team before offering iodine based contrast media to adults on renal replacement therapy including people with kidney transplant. Committee members did not consider it necessary to routinely have this discussion about people with other contraindications to intravenous fluids because it agreed that this decision was better made by individual clinicians. Therefore, the committee agreed to remove other contraindications to intravenous fluids from the recommendation.

Cost effectiveness and resource use

The committee discussed the economic evidence relating to the use of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults. As no published economic evaluations that were relevant to the review question had been found, the committee’s discussion focused on the economic model that was developed for this guideline to be directly applicable to the decision problem. The results of the model were presented to the committee, including probabilistic and deterministic sensitivity analyses and scenario analyses according to elective and emergency presentations (varying baseline risk of CI-AKI and costing assumptions). The committee understood that the model outputs directly reflect the results of the NMA, and the limitations of the NMA discussed above should be kept in mind when considering the model results.

Cost-effectiveness results indicated that sodium bicarbonate (oral) with oral fluids dominates all other interventions. This was the case across the base case, sensitivity and subgroup

analyses. However, the committee was cautious of this result given the prior discussions of the NMA evidence; the credible interval surrounding the point estimate for sodium bicarbonate (oral) with oral fluids was very wide, and there was only a single trial arm (comprising 21 participants) contributing to the evidence base. The committee ruled out recommending this intervention as it could not draw any conclusions about its effectiveness due to the high degree of uncertainty in the evidence.

Discussions then moved on to the other interventions. The only regimen that, at its point estimate, is associated with fewer episodes of AKI than oral fluids alone is sodium chloride 0.9% with sodium bicarbonate (IV). Therefore, the committee was interested to see how cost-effectiveness results for this strategy compared with oral fluids. In focusing on this comparison, the committee was not attempting to assess the cost effectiveness of the single regimen of sodium chloride 0.9% with sodium bicarbonate (IV); rather, committee members were interested to explore how the best-performing of all intravenous regimens compared with oral fluids alone, as this gave an indication of the best value that could be gained from an intravenous hydration strategy. Similarly, the committee also found it helpful to review the results of grouped probabilistic sensitivity analyses. It noted that almost half the strategies simulated (8 of 17) are consistent with the existing recommendation – that is, they include intravenous sodium chloride 0.9%, sodium bicarbonate or both. The committee understood that, in the presence of substantial uncertainty, this had the effect of dividing the probability mass thinly between several options that cannot be differentiated. As a result, while any 1 of the strategies has a low probability of representing the optimal balance of costs and benefits, there is a much higher chance that 1 or other of them provides best value. Therefore, the committee found it helpful to review the outputs of probabilistic analyses that broke results from 17 strategies down into a simple 3-way split: (i) oral fluids alone, (ii) intravenous regimens with sodium chloride 0.9% and/or sodium bicarbonate (as currently recommended), (iii) other options (including oral NAC alone, no hydration regimen and IV sodium chloride 0.45%).

In the base case, sodium chloride 0.9% with sodium bicarbonate (IV) has an ICER of £510,922 per QALY compared with oral fluids. All other interventions are dominated. The committee agreed that this reinforced the results of the NMA – that, for the average person undergoing a contrast-enhanced scan, there is no evidence that, when compared with careful oral hydration, an intravenous regimen provides meaningful benefit.

The committee then reviewed scenario analyses that sought to establish whether the balance of benefits, harms and costs was different in different groups of people – in particular, those undergoing elective scans and those being treated in emergency settings. The major distinction between these 2 scenarios is the baseline risk of CI-AKI. To reflect this, CI-AKI rates from the sodium chloride 0.9% arms of trials from emergency and elective settings were synthesised separately to obtain setting-specific baseline event-rates. In addition, costing assumptions varied between the 2 scenarios: in the elective setting, the analysis assumed that people receiving preoperative intravenous infusions would have to be admitted for up to a day before the procedure; in the emergency setting, it was assumed that people would already be inpatients, so the administration of intravenous fluids would not, by itself, be associated with additional time in hospital.

The committee saw that, for elective patients, intravenous treatment appeared to be even worse value for money than in the base case: the ICER for sodium chloride 0.9% with sodium bicarbonate (IV) versus oral fluids was £655,323 per QALY. In contrast, the higher risk of AKI in emergency settings, coupled with the lower marginal cost of intravenous regimens when extra hospital stay is not relevant, led to results suggesting there may be a cost-effective role for intravenous hydration. In this scenario, the ICER for sodium chloride

0.9% with sodium bicarbonate (IV) versus oral fluids reduced to £16,112 per QALY. However, the committee understood that this result was subject to substantial uncertainty. It saw deterministic sensitivity analysis showing that outputs could be meaningfully affected by plausible variations to a range of parameters – including but not limited to the relative effects of 1 or both of sodium chloride 0.9% with sodium bicarbonate (IV) and oral fluids. Probabilistic results suggested that there is about a 60% chance that 1 or other of the simulated regimens containing intravenous sodium chloride 0.9% and/or intravenous sodium bicarbonate provides best value in the emergency setting.

The committee interpreted these results as showing that, when baseline risks are high, intravenous volume expansion may slightly attenuate the risk of CI-AKI and this may be cost effective, so long as it is not necessary to admit the person for the sole purpose of preparing for their procedure in this way. Committee members agreed that these results are consistent with their experience, but also noted that the analyses are conservative in estimating the benefits of oral fluid regimens: while the costs of admission for intravenous volume expansion are accounted for in the model, it cannot capture other disadvantages of unnecessary hospitalisation, including inconvenience for the patient, and increases in common risks (for example, falls and hospital-acquired infections).

For these reasons, the committee agreed that careful attention to oral hydration should be adequate for all outpatient procedures and many inpatient ones, with intravenous volume expansion reserved for cases at particularly high risk of CI-AKI.

When deciding on which IV intervention to recommend in the high risk population, the committee discussed that although sodium chloride 0.9% with sodium bicarbonate (IV) was the most cost-effective, there were concerns about its practical implementation. They advised that pre-mixed sodium chloride and sodium bicarbonate solutions are not available in the UK and would need to be made up by hospital staff, with additional resource and cost implications. The grouped probabilistic results indicate that regimens containing intravenous sodium chloride 0.9% and/or intravenous sodium bicarbonate provide best value in the emergency setting, and individual packs of sodium chloride 0.9% or sodium bicarbonate (IV) can be easily obtained without the same practical issues.

Other factors the committee took into account

The committee agreed that the evidence was probably sufficient to make negative (‘do not offer’) recommendations with respect to NAC and sodium chloride 0.45%. It discussed whether there would be value in doing so, but agreed that these interventions are seldom used in NHS practice, so there is little to be gained by advising practitioners against choosing them. Instead, the committee focused on its positive recommendations about what should be done.

The committee did not consider any evidence relating to the use of ACE inhibitors and ARBs in people having iodine based contrast media and therefore it was unable to update this recommendation..

Appendices

Appendix A – Review protocols

Review protocol for preventing contrast induced acute kidney injury in at risk adults

ID	Field	Content
0.	PROSPERO registration number	CRD42019133220
1.	Review title	Preventing contrast induced acute kidney injury in at risk adults.
2.	Review question	What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?
3.	Objective	To assess the clinical and cost effectiveness of NAC and/or fluids in preventing CI-AKI in at risk adults.
4.	Searches	The following databases will be searched for clinical searches: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effect (DARE)

		• HTA • Embase • MEDLINE • Medline in process • Medline EPub Ahead of Print The following databases will be searched for cost effectiveness searches: • Medline • Medline in Process • Medline EPub Ahead of Print • Embase • Econlit • NHS EED (legacy records) economic evaluations and quality of life filters applied. Searches will be restricted by:

		• English language • Human studies • Systematic Review filter (clinical searches) • RCT filter (clinical searches) Conference abstracts will be excluded from the search results January 2013 date limit for all interventions except fluid interventions which will have no date limit The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Contrast induced-AKI is uncommon in the general population, with an incidence of 1-2%, and occurs within 72 hours of receiving iodinated contrast media, usually recovering over the following five days. Its incidence increases significantly in patients with risk factors. The risk of CI-AKI may be as high as 25% in patients with a combination of chronic kidney disease (CKD) and diabetes, cardiac failure, older age and exposure to

		nephrotoxic drugs. The CI-AKI Consensus Working Panel has recommended that the risk of CI-AKI becomes clinically important with an eGFR < 60 ml/min/1.73m2. Acutely ill patients with ischaemia, sepsis and/or hypotension are particularly vulnerable to CI-AKI.
6.	Population	Inclusion: Adults (18 and older) who are at risk (as defined by the study author) of contrast induced AKI Exclusion: Pregnant women, renal transplant patients

7.	Intervention/Exposure/Test	• Sodium chloride 0.9% and 0.45% • Sodium bicarbonate • Oral fluids • N-acetylcysteine (NAC) • Balanced electrolyte solutions (Hartmanns, PlasmaLyte) • Other intravenous fluids 1. Combinations of above interventions Key data to be extracted for each intervention: • Agent • Regime • Duration • Dosage (volume per kg per unit time) 2. Both pre- and post- procedure
8.	Comparator/Reference standard/Confounding factors	• Each other • Placebo (for NAC) • No treatment
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs

		Current recommendations are based on strong RCT evidence, so only further RCT evidence is sufficient to change the recommendations.
10.	Other exclusion criteria	• Non-English language studies • Studies in which the type of iodinated contrast used is not specified • Conference abstracts • Theses • Non-human studies
11.	Context	This review will update chapter 6, section 6.2 of the NICE guideline CG169: Acute Kidney Injury

12.	Primary outcomes (critical outcomes)	<u>For the pairwise analysis</u> **Primary outcomes** • Contrast induced AKI (as defined by study (usually 48-72 hours) but diagnosed within 7 days of contrast being given to allow for delays in testing) • CKD progression at 3 months after diagnosis of CI-AKI • Mortality (up to 1 year) • Number of patients needing renal replacement therapy (timescale defined by study authors) • Adverse events (including heart failure, as reported by study) Outcomes used for NMA may not include all of these depending on ability to make meaningful connected networks.
13.	Secondary outcomes (important outcomes)	**Other outcomes of interest:** • Length of hospital stay • Readmission for AKI (within 2 weeks) • Health related quality of life (any measure)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any

		disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from new studies into an excel spreadsheet in a format suitable for uploading to WinBUGS for the purposes of network meta-analysis. Data will also be added to this spreadsheet from studies included in the previous review (this data will be copied from RevMan or RevPal rather than being a de novo extraction). The original review excluded a number of studies with N<80 people. These studies are listed in the excluded studies section of the original review. These previously excluded studies will be added back in if they were excluded only on the basis of a sample size N<80 to ensure consistency between the new data set and the original data set. Study investigators may be contacted for missing data where time and resources allow. Systematic reviews will be used to check that the RCTs they contain have been included.

15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using the Cochrane RoB (2.0) checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of interventional data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

		Meta-analyses will be performed in Cochrane Review Manager V5.3 Hierarchical Bayesian Network Meta-Analysis (NMA) will be performed using WinBUGS version 1.4.3. The models that will be used reflect the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 will be used without substantive alteration to specify synthesis models. Results will be reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 ‘burn-in’ iterations. Three separate chains with different initial values will be used. Non-informative prior distributions will used in all models. Fixed- and random-effects models will be explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC is at least 3 points lower for the random-effects model, it will be used; otherwise, the fixed

		effects model will be considered to provide an equivalent fit to the data in a more parsimonious analysis..
17.	Analysis of sub-groups	If there is heterogeneity in the meta-analysis, and where data allow, subgroup analysis will explore:

		• Risk factor
		  o People with CKD
		  o People with diabetes
		  o Older people >75 years
		  o People with hypovolaemia
		  o People with sepsis
		• Contrast agent
		  o Route of administration
		  ▪ IV
		  ▪ intra-arterial
		  o Type of agent
		  ▪ Ionic
		  ▪ non-ionic
		  o Osmolarity
		  ▪ Low
		  ▪ iso osmolar
		• Patient status
		  o Outpatients
		  o Inpatients (likely to be more unwell and at increased risk)
		  o Acutely ill or in ICU

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]

22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** acutekidneyinjury@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Mr Chris Carmona • Dr Yolanda Martinez • Miss Hannah Nicholas • Ms Andrea Heath		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10117
29.	Other registration details	None
30.	Reference/URL for published protocol	None

31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Contrast induced acute kidney injury, N-acetylcysteine, intravenous fluids
33.	Details of existing review of same topic by same authors	Section 6.2 of the NICE guideline CG169: Acute Kidney Injury. Available at https://www.nice.org.uk/guidance/cg169
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published

		☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

Prioritisation of CI-AKI definitions for pairwise and network meta-analyses

List of CI-AKI definitions to prioritise for pairwise and network meta-analyses

CI-AKI definition	Priority
increase in sCr ≥25% or 44μmol/l	1
increase in sCr ≥25%	2
increase in sCr ≥44μmol/l	3
increase in sCr ≥25% or 44μmol/l or decrease in GFR of ≥5 ml/min	4
decrease in eGFR >25% between 1 to 4 days after contrast	5

(a) sCr: serum creatinine; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias (RoB) Tool version 2.0. individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Some concerns – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence (pairwise analysis)

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one

treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. However, no consensus MIDs were defined and no published MIDs were found.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For mean differences where no other MID was available, an MID of +/- 0.5 standard deviations from the mean value was used (Norman 2003). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

MIDs were used both for assessing imprecision in GRADE and also for assessing clinical importance of treatment effects.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 9

Table 9: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate (some concerns) or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate (some concerns) or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies

GRADE criteria	Reasons for downgrading quality
	(heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed where 10 or more studies were included as part of a single meta-analysis and a funnel plot was produced to graphically assess the potential for publication bias[a].

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

[a] Sterne Jonathan A C, Sutton Alex J, Ioannidis John P A, Terrin Norma, Jones David R, Lau Joseph et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials BMJ 2011; 343 :d4002

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally coherent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following three criteria were met:

- At least three treatment alternatives.
- A sufficiently connected network to enable valid estimates to be made.
- The aim of the review was to produce recommendations on the most effective option, rather than simply an unordered list of treatment alternatives.

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk) with additional models provided by the TSU (see appendix O for NMA models).

Results were reported summarising 50,000 samples from the posterior distribution of each model, having first run and discarded 50,000 ‘burn-in’ iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal(0,10000) priors, and the between-trial standard deviations used in random-effects models were given Uniform(0,5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from studies that were partially or indirectly applicable compared to the protocol, a sensitivity analysis was conducted, excluding those studies from the analysis. Where sufficient studies were available, meta-regression was undertaken to explore the effect of study level covariates.

Choice of outcomes for network meta-analysis

Number of diagnoses of CI-AKI within 5 days of the an iodine based contrast media being given intravenously or intra-arterially was selected as the most appropriate outcome to

prioritise because there were sufficient numbers of trials to form a connected network that included the majority of interventions.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken (Table 10). While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 10: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effects model. For network meta-analyses conducted under a frequentist framework, the network was downgraded one level if the I^2 was greater than 50%. In addition, under both frameworks, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available.

Appendix C – Literature search strategies

RQ: What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?

Sources searched to identify the clinical evidence

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	1/04/2019	Cochrane Central Register of Controlled Trials Issue 4 of 12, April 2019	446
Cochrane Database of Systematic Reviews (CDSR)	1/04/2019	Cochrane Database of Systematic Reviews Issue 4 of 12, April 2019	11
Database of Abstracts of Reviews of Effect (DARE)	1/04/2019	CRD	16
Embase (Ovid)	8/04/2019	Embase 1974 to 2019 Week 14	396
MEDLINE (Ovid)	8/04/2019	Ovid MEDLINE(R) 1946 to April 05, 2019	277
MEDLINE In-Process (Ovid)	1/04/2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to March 29, 2019	37
MEDLINE Epub Ahead of Print	1/04/2019	Ovid MEDLINE(R) Epub Ahead of Print March 29, 2019	4
Health Technology Assessment (HTA Database)	1/04/2019	CRD	0
Total after de-duplication			592

Search strategies

Database: Medline
Strategy used: 1 exp Acute Kidney Injury/ (42761) 2 (contrast-induced* or radiocontrast-induced* or ci).tw. (432886) 3 1 and 2 (2583) 4 Contrast Media/ae (9289) 5 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (8829)

Database: Medline

6 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (529)
7 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (40)
8 (contrast* adj4 (nephropath* or nephrotoxi*)).tw. (2580)
9 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (297)
10 or/3-9 (19554)
11 Acetylcysteine/ (12581)
12 Sodium Chloride/ (57460)
13 Bicarbonates/ (21465)
14 Saline Solution, Hypertonic/ (5470)
15 Saline*.tw. (152324)
16 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (514653)
17 (sodium adj2 (chloride* or bicarbonat*)).tw. (22711)
18 or/11-17 (737710)
19 exp Fluid Therapy/ (19118)
20 Electrolytes/ (24768)
21 (balance* adj2 electrolyte* adj2 solution*).tw. (201)
22 fluid*.tw. (390025)
23 oral* rehydrat*.tw. (2680)
24 (Hartmann* or PlasmaLyte).tw. (3287)
25 or/19-24 (425775)
26 (MEDLINE or pubmed).tw. (137811)
27 systematic review.tw. (97376)
28 systematic review.pt. (103766)
29 meta-analysis.pt. (99181)
30 intervention*.ti. (110298)
31 or/26-30 (327427)
32 randomized controlled trial.pt. (479116)
33 randomi?ed.mp. (737113)
34 placebo.mp. (184329)
35 or/32-34 (786792)
36 31 or 35 (1019975)
37 and/10,18,36 (517)
38 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).ed. (5209038)
39 37 and 38 (182)
40 and/10,25,36 (178)
41 39 or 40 (306)
42 limit 41 to english language (285)
43 animals/ not humans/ (4533573)
44 42 not 43 (277)

Database: MiP/Epubs

Strategy used:

1 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (139)
2 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (16)
3 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (1)
4 (contrast* adj4 (nephropath* or nephrotoxi*)).tw. (43)
5 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (3)
6 or/1-5 (164)
7 Saline*.tw. (2018)
8 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (7274)
9 (sodium adj2 (chloride* or bicarbonat*)).tw. (303)
10 or/7-9 (9464)
11 (balance* adj2 electrolyte* adj2 solution*).tw. (1)
12 fluid*.tw. (7613)
13 oral* rehydrat*.tw. (17)
14 (Hartmann* or PlasmaLyte).tw. (54)
15 or/11-14 (7676)
16 (MEDLINE or pubmed).tw. (6225)
17 systematic review.tw. (5697)
18 systematic review.pt. (17)
19 meta-analysis.pt. (5)
20 intervention*.ti. (3732)
21 or/16-20 (12240)
22 randomized controlled trial.pt. (1)
23 randomi?ed.mp. (12537)
24 placebo.mp. (3006)
25 or/22-24 (13615)
26 21 or 25 (22956)
27 and/6,10,26 (4)
28 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dt. (285027)
29 27 and 28 (4)
30 and/6,15,26 (1)
31 29 or 30 (4)
32 limit 31 to english language (4)

Database: Embase

Strategy used:

1 exp acute kidney failure/ (71966)

Database: Embase
2 exp acute kidney tubule necrosis/ (4531)
3 1 or 2 (75020)
4 (contrast-induced* or radiocontrast-induced* or ci).tw. (746179)
5 3 and 4 (6655)
6 contrast medium/ae (5571)
7 contrast induced nephropathy/ (4314)
8 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (14398)
9 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (1045)
10 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (60)
11 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (357)
12 or/5-11 (27080)
13 acetylcysteine/ (33716)
14 sodium chloride/ (171848)
15 bicarbonate/ (45173)
16 hypertonic solution/ (3912)
17 Saline*.tw. (222699)
18 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (693221)
19 (sodium adj2 (chloride* or bicarbonat*)).tw. (30535)
20 or/13-19 (1044216)
21 exp infusion fluid/ (29634)
22 oral rehydration therapy/ (2559)
23 electrolyte/ (36221)
24 acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/ (312)
25 (balance* adj2 electrolyte* adj2 solution*).tw. (254)
26 fluid*.tw. (544967)
27 oral* rehydrat*.tw. (3031)
28 (Hartmann* or PlasmaLyte).tw. (5022)
29 or/21-28 (605613)
30 (MEDLINE or pubmed).tw. (215134)
31 exp systematic review/ or systematic review.tw. (239844)
32 meta-analysis/ (159213)
33 intervention*.ti. (175512)
34 or/30-33 (559086)
35 random:.tw. (1390441)
36 placebo:.mp. (428367)
37 double-blind:.tw. (195979)
38 or/35-37 (1636073)
39 34 or 38 (2019847)
40 and/12,20,39 (1017)
41 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dc. (9825657)
42 40 and 41 (426)

Database: Embase

43 and/12,29,39 (234)
44 42 or 43 (600)
45 limit 44 to english language (582)
46 limit 45 to (conference abstract or conference paper) (172)
47 45 not 46 (410)
48 nonhuman/ not (human/ and nonhuman/) (4339559)
49 47 not 48 (396)

Database: Cochrane Library (CDSR and CENTRAL)

Strategy used:

#1 [mh "Acute Kidney Injury"]
#2 (contrast-induced* or radiocontrast-induced* or ci):ti,ab
#3 #1 and #2
#4 MeSH descriptor: [Contrast Media] this term only and with qualifier(s): [adverse effects - AE]
#5 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*):ti,ab
#6 (contrast-induced near/4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)):ti,ab
#7 (radiocontrast-induced near/4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)):ti,ab
#8 (contrast* near/4 (nephropath* or nephrotoxi*)):ti,ab
#9 (radiocontrast* near/4 (nephropath* or nephrotoxi*)):ti,ab
#10 {OR #3-#9}
#11 [mh ^Acetylcysteine]
#12 [mh ^"Sodium Chloride"]
#13 [mh ^Bicarbonates]
#14 [mh ^"Saline Solution, Hypertonic"]
#15 Saline*:ti,ab
#16 (Nacet* or acet* or n-acet* or parvolex or mucomyst):ti,ab
#17 (sodium near/2 (chloride* or bicarbonat*)):ti,ab
#18 {OR #11-#17}
#19 [mh "Fluid Therapy"]
#20 [mh ^Electrolytes]
#21 (balance* near/2 electrolyte* near/2 solution*):ti,ab
#22 fluid*:ti,ab
#23 oral* rehydrat*:ti,ab
#24 (Hartmann* or PlasmaLyte):ti,ab
#25 {OR #19-#24}
#26 #10 and #18 with Cochrane Library publication date Between Jan 2013 and Apr 2019
#27 #10 and #25
#28 #26 or #27
#29 "conference":pt
#30 #28 not #29

Database: Cochrane Library (CDSR and CENTRAL)

Database: DARE/HTA

Strategy used:

1 MeSH DESCRIPTOR acute kidney injury EXPLODE ALL TREES
2 ((contrast-induced* or radiocontrast-induced* or ci))
3 #1 AND #2
4 MeSH DESCRIPTOR contrast media WITH QUALIFIER AE
5 ((ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*))
6 (contrast-induced) AND ((aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*))
7 (radiocontrast-induced) AND ((aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*))
8 (contrast) AND ((nephropath* or nephrotoxi*))
9 (radiocontrast) AND ((nephropath* or nephrotoxi*))
10 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11 MeSH DESCRIPTOR Acetylcysteine
12 MeSH DESCRIPTOR Sodium Chloride
13 MeSH DESCRIPTOR Bicarbonates
14 MeSH DESCRIPTOR Saline Solution, Hypertonic
15 (Saline*)
16 ((Nacet* or acet* or n-acet* or parvolex or mucomyst))
17 (Sodium) AND ((chloride* or bicarbonat*))
18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19 MeSH DESCRIPTOR Fluid therapy EXPLODE ALL TREES
20 MeSH DESCRIPTOR Electrolytes
21 (balance*) AND (electrolyte*) AND (solution*)
22 (fluid*)
23 (oral* rehydrat*)
24 ((Hartmann* or PlasmaLyte))
25 #19 OR #20 OR #21 OR #22 OR #23 OR #24
26 #10 AND #18
27 (#26) IN DARE, HTA FROM 2013 TO 2019
28 #10 AND #25
29 (#28) IN DARE, HTA
30 #27 OR #29

Sources searched to identify economic evaluations

Economics	Date searched
MEDLINE (Ovid)	9th April 2019
MEDLINE in Process (Ovid)	9th April 2019
MEDLINE Epub Ahead of Print	9th April 2019
Embase (Ovid)	9th April 2019
EconLit (Ovid)	9th April 2019
NHS Economic Evaluation Database (NHS EED) (legacy database)	9th April 2019

Search strategies

Database: Medline
Strategy used: 1 exp Acute Kidney Injury/ (42766) 2 (contrast-induced* or radiocontrast-induced* or ci).tw. (433052) 3 1 and 2 (2583) 4 Contrast Media/ae (9291) 5 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (8830) 6 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (529) 7 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (40) 8 (contrast* adj4 (nephropath* or nephrotoxi*)).tw. (2581) 9 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (297) 10 or/3-9 (19556) 11 Acetylcysteine/ (12582) 12 Sodium Chloride/ (57464) 13 Bicarbonates/ (21466) 14 Saline Solution, Hypertonic/ (5470) 15 Saline*.tw. (152339) 16 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (514734) 17 (sodium adj2 (chloride* or bicarbonat*)).tw. (22715) 18 or/11-17 (737812) 19 exp Fluid Therapy/ (19121) 20 Electrolytes/ (24769) 21 (balance* adj2 electrolyte* adj2 solution*).tw. (201) 22 fluid*.tw. (390102) 23 oral* rehydrat*.tw. (2680) 24 (Hartmann* or PlasmaLyte).tw. (3287) 25 or/19-24 (425852) 26 Economics/ (27020) 27 exp "Costs and Cost Analysis"/ (223430) 28 Economics, Dental/ (1902) 29 exp Economics, Hospital/ (23455) 30 exp Economics, Medical/ (14090)

Database: Medline	
31	Economics, Nursing/ (3986)
32	Economics, Pharmaceutical/ (2855)
33	Budgets/ (11084)
34	exp Models, Economic/ (13983)
35	Markov Chains/ (13310)
36	Monte Carlo Method/ (26563)
37	Decision Trees/ (10506)
38	econom$.tw. (216611)
39	cba.tw. (9519)
40	cea.tw. (19500)
41	cua.tw. (927)
42	markov$.tw. (16463)
43	(monte adj carlo).tw. (27925)
44	(decision adj3 (tree$ or analys$)).tw. (11859)
45	(cost or costs or costing$ or costly or costed).tw. (420258)
46	(price$ or pricing$).tw. (30693)
47	budget$.tw. (22163)
48	expenditure$.tw. (45624)
49	(value adj3 (money or monetary)).tw. (1909)
50	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3332)
51	or/26-50 (855405)
52	"Quality of Life"/ (174050)
53	quality of life.tw. (205190)
54	"Value of Life"/ (5642)
55	Quality-Adjusted Life Years/ (10861)
56	quality adjusted life.tw. (9490)
57	(qaly$ or qald$ or qale$ or qtime$).tw. (7804)
58	disability adjusted life.tw. (2296)
59	daly$.tw. (2120)
60	Health Status Indicators/ (22807)
61	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (20770)
62	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1240)
63	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4349)
64	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)
65	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (368)
66	(euroqol or euro qol or eq5d or eq 5d).tw. (7484)
67	(qol or hql or hqol or hrqol).tw. (38930)
68	(hye or hyes).tw. (58)
69	health$ year$ equivalent$.tw. (38)
70	utilit$.tw. (155766)
71	(hui or hui1 or hui2 or hui3).tw. (1179)
72	disutili$.tw. (340)

Database: Medline

73 rosser.tw. (82)
74 quality of wellbeing.tw. (11)
75 quality of well-being.tw. (366)
76 qwb.tw. (186)
77 willingness to pay.tw. (3818)
78 standard gamble$.tw. (752)
79 time trade off.tw. (966)
80 time tradeoff.tw. (223)
81 tto.tw. (829)
82 or/52-81 (446712)
83 51 or 82 (1240281)
84 and/10,18,83 (96)
85 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).ed. (5212453)
86 84 and 85 (26)
87 and/10,25,83 (43)
88 86 or 87 (60)
89 limit 88 to english language (51)
90 animals/ not humans/ (4533951)
91 89 not 90 (50)

Database: MiP/Epubs

Strategy used:

1 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (135)
2 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (15)
3 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (1)
4 (contrast* adj4 (nephropath* or nephrotoxi*)).tw. (40)
5 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (3)
6 or/1-5 (158)
7 Saline*.tw. (2003)
8 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (7182)
9 (sodium adj2 (chloride* or bicarbonat*)).tw. (297)
10 or/7-9 (9357)
11 (balance* adj2 electrolyte* adj2 solution*).tw. (2)
12 fluid*.tw. (7568)
13 oral* rehydrat*.tw. (17)
14 (Hartmann* or PlasmaLyte).tw. (58)
15 or/11-14 (7635)
16 econom*.tw. (6178)

Database: MiP/Epubs
17 cba.tw. (56)
18 cea.tw. (331)
19 cua.tw. (22)
20 markov*.tw. (816)
21 (monte adj carlo).tw. (2255)
22 (decision adj3 (tree* or analys*)).tw. (360)
23 (cost or costs or costing* or costly or costed).tw. (12485)
24 (price* or pricing*).tw. (880)
25 budget*.tw. (591)
26 expenditure*.tw. (1193)
27 (value adj3 (money or monetary)).tw. (76)
28 (pharmacoeconomic* or (pharmaco adj economic*)).tw. (51)
29 or/16-28 (21860)
30 quality of life.tw. (6434)
31 quality adjusted life.tw. (332)
32 (qaly* or qald* or qale* or qtime*).tw. (283)
33 disability adjusted life.tw. (91)
34 daly*.tw. (84)
35 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (449)
36 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (79)
37 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (135)
38 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
39 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (6)
40 (euroqol or euro qol or eq5d or eq 5d).tw. (332)
41 (qol or hql or hqol or hrqol).tw. (1270)
42 (hye or hyes).tw. (2)
43 health* year* equivalent*.tw. (0)
44 utilit*.tw. (4921)
45 (hui or hui1 or hui2 or hui3).tw. (23)
46 disutili*.tw. (18)
47 rosser.tw. (0)
48 quality of wellbeing.tw. (1)
49 quality of well-being.tw. (6)
50 qwb.tw. (3)
51 willingness to pay.tw. (141)
52 standard gamble*.tw. (9)
53 time trade off.tw. (30)
54 time tradeoff.tw. (5)
55 tto.tw. (21)
56 or/30-55 (11663)
57 29 or 56 (31881)
58 and/6,10,57 (2)

Database: MiP/Epubs

59 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dt. (282791)
60 58 and 59 (2)
61 and/6,15,57 (0)
62 60 or 61 (2)
63 limit 62 to english language (2)

Database: Embase

Strategy used:

1 exp acute kidney failure/ (71966)
2 exp acute kidney tubule necrosis/ (4531)
3 1 or 2 (75020)
4 (contrast-induced* or radiocontrast-induced* or ci).tw. (746179)
5 3 and 4 (6655)
6 contrast medium/ae (5571)
7 contrast induced nephropathy/ (4314)
8 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw. (14398)
9 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (1045)
10 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw. (60)
11 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw. (357)
12 or/5-11 (27080)
13 acetylcysteine/ (33716)
14 sodium chloride/ (171848)
15 bicarbonate/ (45173)
16 hypertonic solution/ (3912)
17 Saline*.tw. (222699)
18 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw. (693221)
19 (sodium adj2 (chloride* or bicarbonat*)).tw. (30535)
20 or/13-19 (1044216)
21 exp infusion fluid/ (29634)
22 oral rehydration therapy/ (2559)
23 electrolyte/ (36221)
24 acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/ (312)
25 (balance* adj2 electrolyte* adj2 solution*).tw. (254)
26 fluid*.tw. (544967)
27 oral* rehydrat*.tw. (3031)
28 (Hartmann* or PlasmaLyte).tw. (5022)
29 or/21-28 (605613)

Database: Embase	
30	exp Health Economics/ (788191)
31	exp "Health Care Cost"/ (272876)
32	exp Pharmacoeconomics/ (191839)
33	Monte Carlo Method/ (35445)
34	Decision Tree/ (10807)
35	econom$.tw. (327324)
36	cba.tw. (12180)
37	cea.tw. (31923)
38	cua.tw. (1343)
39	markov$.tw. (26602)
40	(monte adj carlo).tw. (42303)
41	(decision adj3 (tree$ or analys$)).tw. (20041)
42	(cost or costs or costing$ or costly or costed).tw. (683195)
43	(price$ or pricing$).tw. (51316)
44	budget$.tw. (35046)
45	expenditure$.tw. (67959)
46	(value adj3 (money or monetary)).tw. (3110)
47	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8163)
48	or/30-47 (1590045)
49	"Quality of Life"/ (418371)
50	Quality Adjusted Life Year/ (23273)
51	Quality of Life Index/ (2585)
52	Short Form 36/ (25191)
53	Health Status/ (118404)
54	quality of life.tw. (384950)
55	quality adjusted life.tw. (17080)
56	(qaly$ or qald$ or qale$ or qtime$).tw. (17531)
57	disability adjusted life.tw. (3412)
58	daly$.tw. (3390)
59	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (38030)
60	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2121)
61	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8388)
62	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (54)
63	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (416)
64	(euroqol or euro qol or eq5d or eq 5d).tw. (17336)
65	(qol or hql or hqol or hrqol).tw. (84264)
66	(hye or hyes).tw. (122)
67	health$ year$ equivalent$.tw. (40)
68	utilit$.tw. (256523)
69	(hui or hui1 or hui2 or hui3).tw. (2029)
70	disutili$.tw. (813)
71	rosser.tw. (110)

Database: Embase

72 quality of wellbeing.tw. (38)
73 quality of well-being.tw. (464)
74 qwb.tw. (234)
75 willingness to pay.tw. (7367)
76 standard gamble$.tw. (1045)
77 time trade off.tw. (1578)
78 time tradeoff.tw. (269)
79 tto.tw. (1499)
80 or/49-79 (880430)
81 48 or 80 (2330456)
82 and/12,20,81 (263)
83 (201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dc. (9825657)
84 82 and 83 (109)
85 and/12,29,81 (81)
86 84 or 85 (179)
87 limit 86 to english language (173)
88 limit 87 to (conference abstract or conference paper) (57)
89 87 not 88 (116)
90 nonhuman/ not (human/ and nonhuman/) (4339559)
91 89 not 90 (115)

Database: Econlit

Strategy used:

1 health*.sh,kw. (52846)
2 related disciplines.sh,kw. (8641)
3 1 or 2 (61487)
4 (contrast-induced* or radiocontrast-induced* or ci).tw,kw. (536)
5 3 and 4 (209)
6 (ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw,kw. (12)
7 (contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw,kw. (0)
8 (radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw,kw. (0)
9 (contrast* adj4 (nephropath* or nephrotoxi*)).tw,kw. (1)
10 (radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw,kw. (0)
11 or/5-10 (221)
12 Saline*.tw,kw. (71)
13 (Nacet* or acet* or n-acet* or parvolex or mucomyst).tw,kw. (42)
14 (sodium adj2 (chloride* or bicarbonat*)).tw,kw. (0)
15 or/12-14 (113)

Database: Econlit

16 (balance* adj2 electrolyte* adj2 solution*).tw,kw. (0)
17 fluid*.tw,kw. (834)
18 oral* rehydrat*.tw,kw. (18)
19 (Hartmann* or PlasmaLyte).tw,kw. (34)
20 or/16-19 (885)
21 11 and 15 (0)
22 11 and 20 (3)
23 21 or 22 (3)

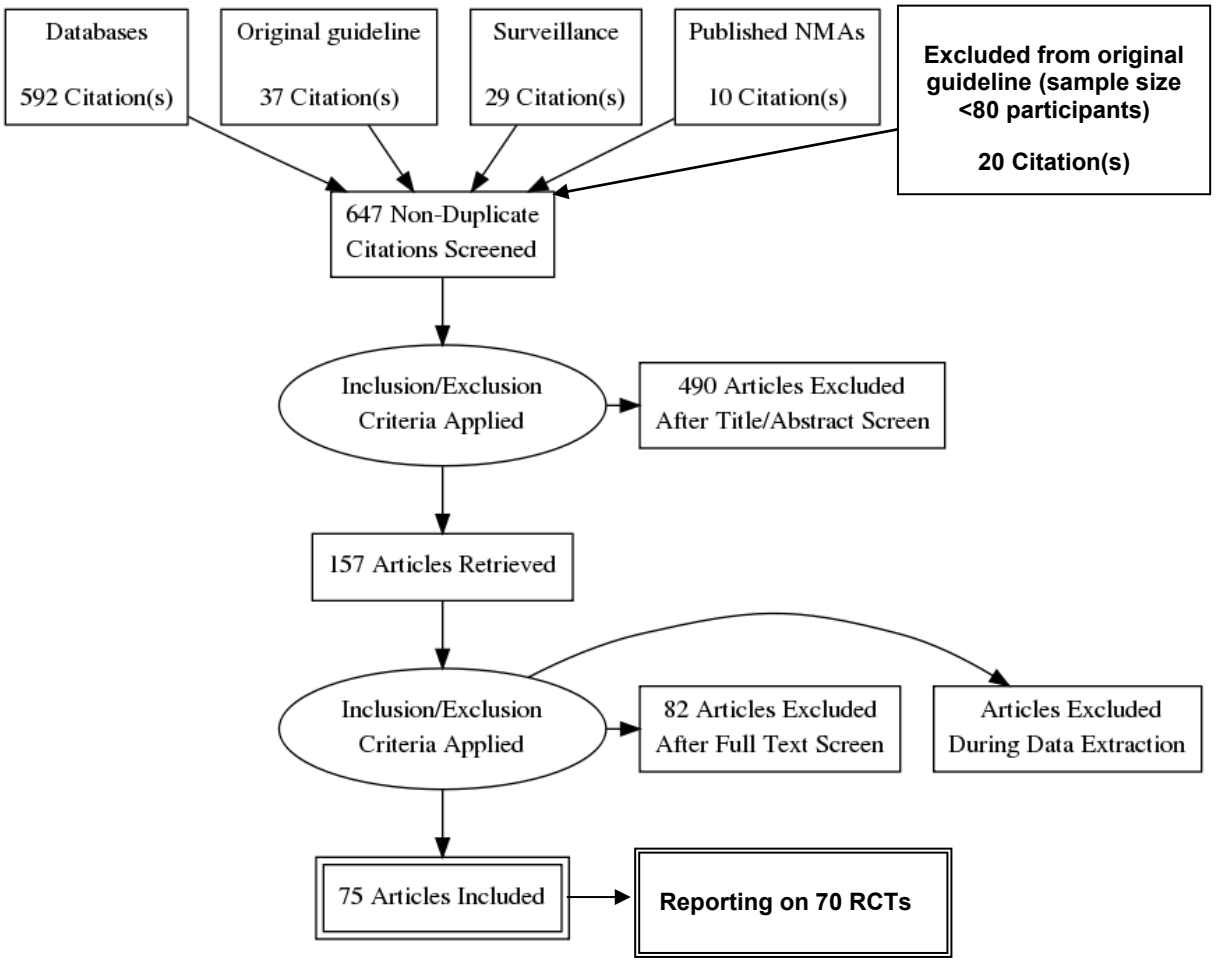
Database: NHS EED

Strategy used:

1 MeSH DESCRIPTOR acute kidney injury EXPLODE ALL TREES
2 ((contrast-induced* or radiocontrast-induced* or ci))
3 #1 AND #2
4 MeSH DESCRIPTOR contrast media WITH QUALIFIER AE
5 ((ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*))
6 (contrast-induced) AND ((aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*))
7 (radiocontrast-induced) AND ((aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*))
8 (contrast) AND ((nephropath* or nephrotoxi*))
9 (radiocontrast) AND ((nephropath* or nephrotoxi*))
10 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11 MeSH DESCRIPTOR Acetylcysteine
12 MeSH DESCRIPTOR Sodium Chloride
13 MeSH DESCRIPTOR Bicarbonates
14 MeSH DESCRIPTOR Saline Solution, Hypertonic
15 (Saline*)
16 ((Nacet* or acet* or n-acet* or parvolex or mucomyst))
17 (Sodium) AND ((chloride* or bicarbonat*))
18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19 MeSH DESCRIPTOR Fluid therapy EXPLODE ALL TREES
20 MeSH DESCRIPTOR Electrolytes
21 (balance*) AND (electrolyte*) AND (solution*)
22 (fluid*)
23 (oral* rehydrat*)
24 ((Hartmann* or PlasmaLyte))
25 #19 OR #20 OR #21 OR #22 OR #23 OR #24
26 #10 AND #18
27 (#26) IN NHSEED FROM 2013 TO 2019
28 #10 AND #25
29 (#28) IN NHSEED
30 #27 OR #29

Database: NHS EED

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Adolph 2008

Bibliographic Reference	Adolph, Esther; Holdt-Lehmann, Birgit; Chatterjee, Tushar; Paschka, Susanne; Prott, Andreas; Schneider, Henrik; Koerber, Thomas; Ince, Huseyin; Steiner, Michael; Schuff-Werner, Peter; Nienaber, Christoph A.; Renal Insufficiency Following Radiocontrast Exposure Trial (REINFORCE): a randomized comparison of sodium bicarbonate versus sodium chloride hydration for the prevention of contrast-induced nephropathy; Coronary artery disease; 2008; vol. 19 (no. 6); 413-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Single centre, cardiology department
Study dates	2005 - 2006
Duration of follow-up	48 hours
Sources of funding	None reported
Inclusion criteria	Serum creatinine Two sCr levels >106µmol/l within 12 weeks of angiography that differed by <5% Age >18 years old
Exclusion criteria	Other conditions Acute MI requiring primary or rescue coronary intervention; Thyroid dysfunction; Pregnancy; Uncontrolled hypertension; Life-limiting concomitant disease; Pulmonary oedema; Chronic RRT Allergy Allergy to trial medication Contrast Exposure to contrast medium in last 7 days Medications Administration of dopamine, mannitol, fenoldopam, NAC
Sample size	N=145 patients
Split between study groups	Group 1 -Sodium bicarbonate n=71 Group 2 - 0.9% sodium chloride n=74

Loss to follow-up	3
Mean age (SD)	72 (6.7)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 138 ± 38.9
Interventions	Intervention dose Sodium bicarbonate (154mEq/L in 5% dextrose) Intervention route IV Intervention pre-contrast 2ml/kg/h for 2h Intervention post-contrast 1ml/kg/h for 6h Contrast type Iso-osmolar Contrast name iodixanol
Outcome measures	Contrast induced AKI increase in sCr ≥25% or 44µmol/l CKD progression NR Mortality NR Number of patients needing RRT Adverse events NR Length of hospital stay days Readmission for AKI NR Health related quality of life NR

Study arms

	IV sodium chloride 0.9% (N = 76)

Sample size	145
Loss to follow-up	2
% Female	18.9
Mean age (SD)	72.7 (6.6)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 138.8 (31.8) % CKD 100 % Diabetes 28.3 % Hypertension 87.8 % ACEI NR % NSAIDs NR Notes Baseline serum creatinine was calculated from mg/dl by NCGC (x88.4)
Interventions	Intervention dose 154mEq/L in 5% dextrose Intervention route IV Intervention pre-contrast 2ml/kg/h for 2h Intervention during contrast NR Intervention post-contrast 1ml/kg/h for 6h Contrast type Nonionic, iso-osmolar Contrast name iodixanol Contrast dose, ml, mean (SD) 138 (52)

	Contrast procedure elective diagnostic or interventional angiography

IV sodium bicarbonate (N = 72)

Sample size	72
Loss to follow-up	1
% Female	25.4
Mean age (SD)	70.1 (8.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 136.1 (45.1) % CKD 100 % Diabetes 36.6 % Hypertension 83.1 % ACEI NR % NSAIDs NR Notes Baseline serum creatinine was calculated from mg/dl by NCGC (x88.4)
Interventions	Intervention dose 154mEq/L in 5% dextrose Intervention route IV Intervention pre-contrast 2ml/kg/h for 2h Intervention during contrast NR Intervention post-contrast 1ml/kg/h for 6h Contrast type nonionic, iso-osmolar

		Contrast name iodixanol Contrast dose, ml, mean (SD) 141 (50) Contrast procedure elective diagnostic or interventional angiography

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(although unclear if allocation concealment)

Overall Directness

Directly applicable

Agrawal 2004

Bibliographic Reference	Agrawal, M.; Wodlinger, A.M.; Huggins, C.E.; Tudor, G.E.; Pieper, J.A.; O?Reilly, K.P.; Denu-Ciocca, C.J.; Stouffer, G.A.; Ohman, E.M.; Effect of N-Acetylcysteine on Serum Creatinine Concentration in Patients with Chronic Renal Insufficiency Who Are Undergoing Coronary Angiography; Heart Drug; 2004; vol. 4 (no. 2); 87-91

Study details

Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Hospital
Study dates	February to November 2002
Duration of follow-up	48h
Sources of funding	None
Inclusion criteria	Age 18 years or older Other Renal insufficiency as defined by a serum Cr ≥1.5 mg/dl or creatinine clearance ≤50 ml/min
Exclusion criteria	Other conditions Cardiogenic shock Contrast Exposure to intravenous contrast dye in the 72 h before enrollment History of dialysis Hemodialysis or peritoneal dialysis Procedures Emergent coronary angiography other Inability to take oral medications, hypersensitivity to acetylcysteine, previous organ transplantation
Sample size	25
Loss to follow-up	None

Interventions	Contrast type Non-ionic Contrast name Omnipaque Contrast procedure Coronary angiography and/or percutaneous coronary intervention
Outcome measures	Contrast induced AKI Either a 0.5-mg/dl increase in serum creatinine concentration or a 25% increase in serum creatinine concentration at 48 h

Study arms

Oral NAC + IV sodium chloride 0.45% (N = 11)

Pre-contrast: oral NAC 800 mg 12h prior angiography, 600 mg 2h prior angiography, with IV sodium chloride 0.45% 1 ml/kg for 12h before and during angiography. Post-contrast: oral NAC 600 mg 6h after angiography, with IV sodium chloride 0.45% 1 ml/kg for 12h after angiography (unless there was concern that this might precipitate pulmonary edema).

% Female	18
Mean age (SD)	65.5
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 141.44 µmol/l % Diabetes 36 % Hypertension 100 % ACEI 82
Interventions	Contrast dose, ml, mean (SD) 187.7

IV sodium chloride 0.45% (N = 14)

	Pre-contrast: matching placebo, with IV sodium chloride 0.45% 1 ml/kg for 12h before and during angiography. Post-contrast: matching placebo, with IV sodium chloride 0.45% 1 ml/kg for 12h after angiography (unless there was concern that this might precipitate pulmonary edema).	
	% Female	43
	Mean age (SD)	62.8
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 150.28 % Diabetes 57 % Hypertension 86 % ACEI 69
	Interventions	Contrast dose, ml, mean (SD) 170

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if allocation concealment; no protocol cited)

Overall Directness

Directly applicable

Akyuz 2014

Bibliographic Reference	Akyuz, Sukru; Karaca, Mehmet; Kemaloglu Oz, Tugba; Altay, Servet; Gungor, Baris; Yaylak, Baris; Yazici, Selcuk; Ozden, Kivilcim; Karakus, Gultekin; Cam, Nese; Efficacy of oral hydration in the prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography or intervention; Nephron. Clinical practice; 2014; vol. 128 (no. 12); 95-100

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey;
Study setting	Three cardiology departments (inpatient);
Study dates	January 2012 - January 2013
Duration of follow-up	48 hours following administration of contrast (for AKI);; 30 day follow up for mortality outcomes or need for dyalysis;
Sources of funding	No funding source acknowledged;
Inclusion criteria	Age ≥70 years Diabetes mellitus Type 2 diabetes mellitus History of chronic heart failure or systolic dysfunction Anaemia hyperuricaemia

Exclusion criteria	Other conditions Type 1 diabetes mellitus; acute ST elevation myocardial infarction; unstable angina pectoris or non-ST elevation myocardial infarction for whom emergent/urgent interventional strategy should be implemented; AKI of alternative etiology; hypervolemic hyponatraemia; active decompensated heart failure. Allergy Known allergy for contrast media Contrast Recent exposure to contrast in last 3 days Medications Use of nephrotoxic drugs over previous 7 days Age <18 years History of dialysis Pregnancy or breastfeeding Related conditions AKI of alternative etiology Blood pressure > 180/110 mm Hg

Study arms

	Oral hydration (N = 116) Encouraged to drink as much spring or tap water before procedure 12 - 2 hours before procedure

Study setting	Three cardiology departments;
Sample size	116;
Loss to follow-up	None reported;
% Female	28
Mean age (SD)	63.5;± 10.8
Condition specific characteristics	% Diabetes Type 2 diabetes: 58% % Hypertension

	68% % ACEI 66 Baseline serum creatinine, mg/dl, median (IQR) 0.90 (0.30)
Interventions	Intervention dose encouraged to drink as much as possible Intervention route oral Intervention pre-contrast starting at least 12 hours to 2 hours prior to intervention Intervention post-contrast also encouraged to drink 12 hours post procedure Contrast type non-ionic low osmolar Contrast name Iopromide (Ultravist) Contrast dose, ml, mean (SD) 107 (70) Contrast procedure Coronary angiography and/or percutaneous coronary intervention Intervention (more details) Spring or tap water used. For patients with heart failure dosage was 1.5 to 2 litres a day
Outcome measures	Contrast induced AKI >25% relative or ≥0.5 mg/dl increase in SCr Mortality Number of patients needing RRT Requiring dialysis within 30 days post procedure Adverse events

IV Sodium Chloride 0.9% (N = 109)

Duration of follow-up	48 hours following administration of contrast (for AKI);; 30 day follow up for mortality outcomes or need for dialysis;
Sample size	109
Loss to follow-up	None reported;

	% Female	34
	Mean age (SD)	63.2 (10.8)
	Condition specific characteristics	% Diabetes Type 2 diabetes: 63 % Hypertension 73 % ACEI 74 Baseline serum creatinine, mg/dl, median (IQR) 0.90 (0.40)
	Interventions	Intervention dose 1 ml/kg/h Intervention route IV Intervention pre-contrast for 12 hours Intervention post-contrast for 12 hours post contrast Contrast type non-ionic low-osmolar Contrast name Iopromide (Ultravist) Contrast dose, ml, mean (SD) 107 (70) Contrast procedure Coronary angiography and/or percutaneous coronary intervention Intervention (more details) ease in preparation. Consumption of additional fluids was allowed freely in the IV group and total volume of hydration was reported as the sum of the oral and and IV volume intake. For patients with heart failure dosage was 0.5 mg/kg/h
	Outcome measures	Contrast induced AKI >25% relative or ≥0.5 mg/dl increase in SCr Mortality Number of patients needing RRT equiring dialysis within 30 days post procedure Adverse events

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Albabtain 2013

Bibliographic Reference	Albabtain, Monirah A.; Almasood, Ali; Alshurafah, Hytham; Alamri, Hussain; Tamim, Hani; Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-Induced nephropathy: a prospective randomized study; Journal of interventional cardiology; 2013; vol. 26 (no. 1); 90-6

Study details

Study location	Saudi Arabia
Study setting	Prince Sultan Cardiac Center in Riyadh

Study dates	Unclear: Over a two-year period
Duration of follow-up	up to 5 days following procedure
Sources of funding	none reported
Inclusion criteria	Age at least 18 years of age CIN at risk of CIN, defined as having one of the following criteria on admission: serum creatinine ≥1.3 mg/dL (115 mmol/L) or were on diabetes mellitus medication.
Exclusion criteria	Other conditions known acute renal failure, end-stage renal disease requiring dialysis Contrast intravascular administration of contrast medium within the previous 6 days, anticipated re-administration of contrast medium within the following 6 days Medications use of Vitamin C supplements on a daily basis during the week before the procedure, or inability to administer the study medication at least 2 hours before the procedure.
Sample size	243
Loss to follow-up	none reported
Interventions	Contrast type Ioxaglate, a low-osmolality ionic contrast medium Contrast name Hexabrix Contrast dose, ml, mean (SD) 600 mOsmol per kg of water Contrast procedure coronary angiography or PCI
Outcome measures	CIN development of CIN or its definition components as measured 4–5 days after procedure. CIN was defined by an absolute increase of serum creatinine concentration of at least 0.5 mg/dL or a relative decrease of creatinine clearance of at least 25% from the baseline value measured 4 to 5 days after procedure.

Study arms

Oral NAC + sodium chloride 0.9% (N = 58)

NAC orally 600 mg twice daily for 2 days starting the evening before the procedure. Ascorbic acid, supplied as effervescent tablets, 3 g 2 hours before the angiogram, 2 g after the angiogram, and 2 g 24 hours after the angiogram

% Female	29.3%
Mean age (SD)	64.0 (SD 11.0) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 111.4 (SD 38.0) umol/L % Diabetes 86.2% % Hypertension 62.1% % ACEI 69.0% % NSAIDs 8.6%

IV sodium chloride 0.9% (N = 66)

Normal saline was started in all patients at a rate of 50 to 125 mL/h IV from the time of randomization until at least 6 hours after the procedure.

% Female	18.2%
Mean age (SD)	59.8 (SD10.8) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 107.8 (SD 35.4) umol/L % Diabetes 79.7% % Hypertension 53.1% % ACEI 70.3% % NSAIDs 10.9%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Allaqaband 2002

Bibliographic Reference	Allaqaband S; Tumuluri R; Malik AM; Gupta A; Volkert P; Shalev Y; Bajwa TK; Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy.; Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions; 2002; vol. 57 (no. 3)

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA

Study setting	Clinical secondary care centre
Duration of follow-up	up to 48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine baseline creatinine ≥ 136.8 umol/L or an estimated creatinine clearance of ≤60 ml/min Other scheduled to undergo cardiovascular interventions requiring the use of radio contrast
Sample size	85
Loss to follow-up	none reported
Interventions	Contrast type Low osmolar, non-ionic Contrast name Iodixanol Contrast procedure participants were undergoing cardiovascular interventions requiring radio contrast
Outcome measures	Contrast induced AKI at 48 hours, defined as absolute increase in serum creatinine level of at least 44.2 umol/L

Study arms

Oral NAC + IV sodium chloride 0.45% (N = 45)

Pre-procedure 600mg twice daily in the day before procedure and continuing throughout day of procedure, with 0.45% sodium chloride 1ml/kg/hr for 12 hours prior to procedure. Post-contrast: 0.45% sodium chloride 1ml/kg/hr for 12 hours.

% Female	37.8%
Mean age (SD)	70 (SD10) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 194.5 (SD 64.5) umol/L % Diabetes

	70% % Hypertension 80% % ACEI 50%
Interventions	Contrast type Low osmolar, non-ionic Contrast name Iodixanol Contrast dose, ml, mean (SD) 1.52 (SD 0.81) Contrast procedure participants were undergoing cardiovascular interventions requiring radio contrast

IV sodium chloride (N = 40)

Pre-procedure 0.45% sodium chloride 1ml/kg/hr for 12 hours prior to procedure. Post-contrast: 0.45% sodium chloride 1ml/kg/hr for 12 hours.

% Female	40%
Mean age (SD)	71 (SD 10) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 179.5 (SD 42.4) umol/L % Diabetes 43% % Hypertension 92% % ACEI 65%
Interventions	Contrast type Low osmolar, non-ionic Contrast name Iodixanol Contrast dose, ml, mean (SD) 1.47 (SD 0.90) Contrast procedure

		participants were undergoing cardiovascular interventions requiring radio contrast

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unblinded; unclear if allocation concealment; per-protocol analysis; and unclear if protocol finalized in sufficient detail prior to availability of outcome data.)

Overall Directness

Directly applicable

Aslanger 2012

Bibliographic Reference	Aslanger, E.; Uslu, B.; Akdeniz, C.; Polat, N.; Cizgici, Y.; Oflaz, H.; Intrarenal application of N-acetylcysteine for the prevention of contrast medium-induced nephropathy in primary angioplasty; Coronary artery disease; 2012; vol. 23 (no. 4); 265-270

Study details

Study location	Turkey
Study setting	single centre
Study dates	January 2007 - January 2009
Duration of follow-up	72 hours
Sources of funding	none reported
Inclusion criteria	Age at least 30 days of age Other Patients with STEMI undergoing coronary angiography within 24h of symptom onset
Exclusion criteria	Allergy Known NAC hypersensitivity History of dialysis chronic dialysis
Sample size	220
Loss to follow-up	18
Interventions	Contrast type low-osmolar, ionic Contrast name ioxaglate Contrast dose, ml, mean (SD) 193 (SD 57) ml Contrast procedure coronary angiography
Outcome measures	Contrast induced AKI at 72 hours, defined as increase in sCr ≥25% or 44µmol/l)

Study arms

	IV NAC + oral NAC + sodium chloride 0.9% (N = 108)

Pre-procedure: single iv bolus NAC of 1200mg during the procedure . (total 6g) Post-procedure: 1200mg NAC orally twice daily for 48h after the procedure. * IV saline 0.9% given as at 1ml/kg/hour for 21 hours (unclear whether this is pre, peri, or post-procedure).

% Female	13%
Mean age (SD)	56.1 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 79.6 (SD 26.5) umol/L % Diabetes 25% % Hypertension 51% % ACEI 88% ACEI or ARB

Sodium chloride 0.9% (N = 99)

Pre-procedure: iv saline bolus of 12 ml during the procedure Post-procedure: placebo capsules for 48h after procedure. * IV saline 0.9% given as at 1ml/kg/hour for 21 hours (unclear whether this is pre, peri, or post-procedure).

% Female	32.4%
Mean age (SD)	57.2 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 76.0 (26.5) umol/L % Diabetes 16% % Hypertension 47% % ACEI 91% ACEI or ARB

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Berwanger 2011

Bibliographic Reference	Berwanger, O.; Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized acetylcysteine for contrast-induced nephropathy trial (ACT); Circulation; 2011; vol. 124 (no. 11); 1250-1259

Study details

Study type	Randomised controlled trial (RCT) *Berwanger (2013) contains replicated data of the diabetes subgroup*
Study location	Brazil;
Study setting	Multicentre (46 sites);

Study dates	September 2008 and July 2010
Duration of follow-up	30 days
Sources of funding	Brazilian Ministry of Health
Inclusion criteria	received imaging Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or PCI Moderate to high CIN risk At least one risk factor for CIN: age >70 years, chronic renal failure (stable serum creatinine concentrations >132.6 µmol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction <0.45, or hypotension
Exclusion criteria	Other conditions ST-segment elevation myocardial infarction Age Women aged under 45 were excluded if they did not use contraceptive methods History of dialysis Pregnancy or breastfeeding
Sample size	2308
Loss to follow-up	2
Interventions	Contrast type high osmolarity, low osmolarity, and iso-osmolar contrast used Contrast name not described Contrast procedure peripheral vascular angiography, coronary diagnostic angiography, and PCI
Outcome measures	Contrast induced AKI a 25% elevation of serum creatinine above baseline between 48 and 96 hours after angiography. Mortality deaths and cardiovascular deaths at 30 days Adverse events "other serious adverse events" Need for dialysis at 30 days

	Composite outcome Deaths or need for dialysis at 30 days

Study arms

oral NAC + IV sodium chloride 0.9% (N = 1172)

NAC: a dose of 1200 mg NAC was administered orally every 12 hours. Two doses before and two doses after the procedure. 0.9% Sodium chloride: 1 mL/kg per hour, from 6 - 12 hours before to 6 - 12 hours after angiography

Inclusion criteria	received imaging Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or PCI Moderate to high CIN risk At least one risk factor for CIN: age 70 years, chronic renal failure (stable serum creatinine concentrations 132.6 mol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction 0.45, or hypotension
Sample size	1172
Loss to follow-up	19 for CIN, and 1;for 30 day outcomes
% Female	38.0
Mean age (SD)	68.0 (10.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) Serum creatinine >132.6 µmol/L: 15.4% % CKD eGFR <30 mL/min: 4.9% % Diabetes 61.2 % Hypertension 86.5 % ACEI 59.6 % NSAIDs 5.4
Interventions	Contrast dose, ml, median (IQR)

	100 (70 - 130)
Outcome measures	Contrast induced AKI Mortality deaths and cardiovascular deaths at 30 days Adverse events "other serious adverse events" Need for dialysis at 30 days Composite outcome Deaths or need for dialysis

placebo + IV sodium chloride 0.9% (N = 1136)

placebo: administered orally every 12 hours, for 2 doses before and 2 doses after the procedure 0.9% Sodium chloride: 1 mL/kg per hour, from 6 - 12 hours before to 6 - 12 hours after angiography

Inclusion criteria	received imaging Patients undergoing coronary or peripheral arterial diagnostic intravascular angiography or PCI Moderate to high CIN risk At least one risk factor for CIN: age 70 years, chronic renal failure (stable serum creatinine concentrations 132.6 mol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction 0.45, or hypotension
Sample size	1136
Loss to follow-up	17 for CIN outcomes, 1 for;
% Female	39.3
Mean age (SD)	68.1 (10.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) Serum creatinine >132.6 µmol/L: 16.0% % CKD eGFR<30 mL/min: 5.5% % Diabetes 59.7 % Hypertension

		85.9 % ACEI 58.2 % NSAIDs Use of NSAIDs >7 days: 5.2%
	Interventions	Contrast dose, ml, median (IQR) 100 (70–130)
	Outcome measures	Contrast induced AKI Mortality deaths and cardiovascular deaths at 30 days Adverse events "other serious adverse events" Need for dialysis at 30 days Composite outcome Deaths or need for dialysis

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Baskurt 2009

Bibliographic Reference	Baskurt, M.; Okcun, B.; Abaci, O.; Dogan, G. M.; Kilickesmez, K.; Ozkan, A. A.; Ersanli, M.; Gurmen, T.; N-acetylcysteine versus N-acetylcysteine + theophylline for the prevention of contrast nephropathy; European Journal of Clinical Investigation; 2009; vol. 39 (no. 9); 793-799

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Hospital
Study dates	Between October 2006 and May 2008
Duration of follow-up	48h
Sources of funding	None
Inclusion criteria	eGFR between 30 and 60 mL min-1 1.73 m-2 Chronic kidney disease moderate degree chronic kidney disease
Exclusion criteria	Other conditions acute coronary syndrome, cardiogenic shock, overt congestive heart failure Contrast recent exposure to radio contrast medium within preceding 14 days Medications patients who were taking any medication that has been shown exerting pharmacokinetic interaction with theophylline [cimetidine, isoproterenol (intravenous), salbutamol, terbutaline, corticosteroids, macrolide antibiotics, fluoroquinolones,

	rifampicin, isoniazid, phenytoin, carbamazepine, barbiturates, antiacids (magnesium/aliminium hydroxide)] Age <21 years History of dialysis chronic haemodialysis treatment Procedures emergent procedures eGFR <30 and ≥60 mL min-1 1.73 m-2 other pregnancy, known allergy to NAC, theophylline or to contrast agents, contraindications to theophylline (history of seizures, arrhythmia resulting in haemodynamic instability and⁄or Lown classification IVa or higher within 24 h before administration of contrast medium)
Sample size	145
Interventions	Contrast type non-ionic, low-osmolality Contrast name Ioversol Contrast procedure elective diagnostic coronary angiography Intervention (more details) This RCT included a third arm with oral NAC + IV sodium chloride 0.9% + theophylline but theophylline was not relevant for this review
Outcome measures	Contrast induced AKI 0.5 mg dL-1 absolute increase in serum creatinine level

Study arms

	oral NAC + IV sodium chloride 0.9% (N = 73) Pre-contrast: oral NAC twice daily the preceding day and the day of angiography, with IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h before contrast exposure. Post-contrast: oral NAC none, IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h after contrast exposure.

Loss to follow-up	None
% Female	36.9

Mean age (SD)	67.9 (9.9)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 122.8 (21.2) % Diabetes 27 % Hypertension 53 % ACEI 74 Baseline eGFR, ml/min per 1.73m2, mean (SD) 48.97 (7.18)
Interventions	Contrast dose, ml, mean (SD) 115.61 (35.2)

IV sodium chloride 0.9% (N = 72)

Pre-contrast: IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h before contrast exposure. Post-contrast: IV sodium chloride 0.9% 1 mL kg-1 h-1 for 12h after contrast exposure.

Loss to follow-up	None
% Female	43.0
Mean age (SD)	67.1 (8.6)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 114.9 (17.6) % Diabetes 33 % Hypertension 59 % ACEI 69 Baseline eGFR, ml/min per 1.73m2, mean (SD) 51.52 (7.21)
Interventions	Contrast dose, ml, mean (SD) 113.54 (37.7)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if allocation concealment; no protocol cited)

Overall Directness

Directly applicable

Boucek 2013

Bibliographic Reference	Boucek, Petr; Havrdova, Terezia; Oliyarnyk, Olena; Skibova, Jelena; Pecenkova, Vera; Pucelikova, Tereza; Sarkady, Darina; Prevention of contrast-induced nephropathy in diabetic patients with impaired renal function: a randomized, double blind trial of sodium bicarbonate versus sodium chloride-based hydration; Diabetes research and clinical practice; 2013; vol. 101 (no. 3); 303-8

Study details

Study type	Randomised controlled trial (RCT)

Study location	Czech Republic;
Study setting	Single setting;
Study dates	April 2008 to February 2012
Duration of follow-up	1 month
Sources of funding	Institute for Clinical and Experimental Medicine (IKEM)
Inclusion criteria	Serum creatinine ≥100 mmol/L Age ≥18 years Diabetes mellitus received imaging a planned procedure with intra-arterial or intravenous use of contrast
Exclusion criteria	Other conditions volume overload with left ventricular failure; uncontrolled hypertension; hemodynamic instability; multiple myeloma Contrast contrast use in the previous 48-h period Medications pre-planned use of any other measure for CIN prevention apart from the NaCl or NaHCO3 infusions History of dialysis or pre-planned dialysis following the contrast-involving procedure Pregnancy or breastfeeding Related conditions History of kidney transplant; acute kidney injury (serum creatinine increase ≥50 µmol/L during the previous 24-h period) Blood pressure hypertension (systolic BP ≥180 or diastolic BP ≥110 mmHg), hemodynamic instability (systolic BP <90 and diastolic BP <50 mmHg) Procedures emergency type of procedure, Serum creatinine ≥500 mmol/L
Sample size	126

Loss to follow-up	6
Interventions	Contrast type low osmolar, nonionic, iodinated Contrast name not reported Contrast procedure not specified "elective radiologic procedure with contrast medium"
Outcome measures	CKD progression development of end stage renal failure at one month Mortality at one month Length of hospital stay Need for dialysis CIN serum creatinine increase of ≥25% and/or ≥44 mmol/L (0.5 mg/dL) within 2 days following administration of contrast

Study arms

	IV sodium chloride 0.9% (N = 62) Sodium chloride: 154 mL of 5.85% sodium chloride to 846 mL of 5% glucose. 1 h immediately before (at the rate of 3 mL/kg/h; limited to a maximal amount of 330 mL) and for 6 hour following contrast (at 1 mL/kg BW/h; limited to a maximum of 660 mL)

Loss to follow-up	3
% Female	25.4
Mean age (SD)	67 (10)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 160 (74) % Diabetes 100 Baseline eGFR, ml/min per 1.73m2, mean (SD) 44.6 (16.9)

Interventions	Contrast dose, ml, mean (SD) 104 (32) Contrast procedure coronary angioplasty: 28.8%; lower limb angiography: 61.0%; other: 10.2%

IV sodium bicarbonate (N = 64)

154 mL of 8.4% sodium bicarbonate to 846 mL of 5% glucose 154 mL of 8.4% sodium bicarbonate to 846 mL of 5% glucose. 1 h immediately before (at the rate of 3 mL/kg/h; limited to a maximal amount of 330 mL) and for 6 hour following contrast (at 1 mL/kg BW/h; limited to a maximum of 660 mL)

Sample size	64
Loss to follow-up	3
% Female	24.6
Mean age (SD)	63 (11)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 170 (84) % Diabetes 100 Baseline eGFR, ml/min per 1.73m2, mean (SD) 43.6 (18.9)
Interventions	Contrast dose, ml, mean (SD) 115 (47) Contrast procedure coronary angiography: 41.0%; lower limb angiography: 54.1%; other: 5.2%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Brar 2008

Bibliographic Reference	Brar SS; Shen AY; Jorgensen MB; Kotlewski A; Aharonian VJ; Desai N; Ree M; Shah AI; Burchette RJ; Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial.; JAMA; 2008; vol. 300 (no. 9)

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Single centre
Study dates	January 2006 - January 2007;
Duration of follow-up	6 months;

Sources of funding	Kaiser Permanente, two people (non-administrative) from Kaiser Permanente helped with manuscript preparation and data collection. 7 of the 9 authors affiliated to Kaiser Permanente (although not the 2 authors involved in the analyses).
Inclusion criteria	Age ≥18 years old eGFR ≤60 ml/min/1.73m2 AND one or more of: diabetes mellitus; history of congestive heart failure; hypertension; or age ≥75 years
Exclusion criteria	Other conditions History of heart transplant; Acutely decompensated heart failure; severe cardiac valvular abnormality Allergy to contrast media Contrast Contrast media within preceding two days Medications Sodium bicarbonate infusion prior to randomisation; Related conditions On RRT; Single functioning kidney; history of renal transplant; Change in eGFR ≥7.5% per day or cumulative change of ≥15% over the prior 2 or more days Procedures Emergency cardiac catheterisation; Intra-aortic balloon counterpulsation
Sample size	353

Study arms

	Sodium bicarbonate (N = 175)
Sample size	175
Loss to follow-up	1 did not undergo angiography. 16 did not have eGFR data.
% Female	37.7
Mean age (SD)	median (IQR):;
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 131.7 ± 31.8 % CKD 100

		% Diabetes 43.4 % Hypertension NR % ACEI 47.2 % NSAIDs NR Baseline eGFR, ml/min per 1.73m2, mean (SD) 47.7 ± 9.8
	Interventions	Intervention dose 150mEq/L in 5% dextrose Intervention route IV Intervention pre-contrast 3ml/kg/h for 1 h Intervention during contrast 1.5ml/kg/h Intervention post-contrast 1.5ml/kg/h for 4h Contrast type low osmolar Contrast name ioxilan Contrast procedure coronary angioplasty Contrast dose, ml, median (IQR) 126 (80 - 214)
	Outcome measures	Contrast induced AKI at 96 hours; reported separately as ≥25% decrease in eGFR; increase in sCr ≥25% or 44 µmol/L CKD progression Number of patients achieving dialysis independence Mortality at 30 days; from 30 days to 6 months Number of patients needing RRT in 6 months Length of hospital stay NR

Sodium chloride 0.9% (N = 178)

Sample size	178
Loss to follow-up	2 did not undergo angiography. 11 did not have eGFR data.
% Female	34.8
Mean age (SD)	median (IQR): 71 (65 - 76);
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 131.7 ± 33.6 % CKD 100 % Diabetes 45.5 % Hypertension NR % ACEI 47.2 % NSAIDs NR Baseline eGFR, ml/min per 1.73m2, mean (SD) 48.3 ± 9.4
Interventions	Intervention dose 0.9% Intervention route IV Intervention pre-contrast 3ml/kg/h for 1h Intervention during contrast 1.5ml/kg/h Intervention post-contrast 1.5 ml/kg/h for 4h

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(large amount of missing laboratory data (>5% per arm) and insufficient information about reasons for missing laboratory data)

Overall Directness

Directly applicable

Briguori 2002

Bibliographic Reference	Briguori C; Manganelli F; Scarpato P; Elia PP; Golia B; Riviezzo G; Lepore S; Librera M; Villari B; Colombo A; Ricciardelli B; Acetylcysteine and contrast agent-associated nephrotoxicity.; Journal of the American College of Cardiology; 2002; vol. 40 (no. 2)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Clinical secondary care centre

Study dates	From September 2000
Duration of follow-up	48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine Impaired renal function (serum creatinine concentration >106.8 umol/L and/or estimated CrCl <70ml/min Other undergoing elective coronary and/or peripheral angiography and/or angioplasty
Sample size	183
Loss to follow-up	0
Interventions	Contrast type Low-osmolar non-ionic Contrast name Iopromide Contrast dose, ml, mean (SD) 0.77 mg/ml, 300 mg iodine/ml Contrast procedure undergoing elective coronary and/or peripheral angiography and/or angioplasty
Outcome measures	Contrast induced AKI at 48 hours, defined as increase in serum creatinine concentration of ≥25% over baseline at 48 hours, or the need for dialysis Renal failure need for RRT

Study arms

	oral NAC + IV sodium chloride 0.45% (N = 92) Pre-procedure: 600mg NAC given twice daily on the day before and day of procedure, with 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours prior to procedure. Post-procedure: 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

% Female	16%

Mean age (SD)	64 (SD9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 134.37 (SD 38.01) umol/L % Diabetes 43% % Hypertension 72% % ACEI 56.5%

IV sodium chloride 0.45% (N = 91)

Pre-procedure: 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours prior to procedure. Post-procedure: 0.45% IV sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

% Female	11% female
Mean age (SD)	64 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 136.14 (SD 31.82) years % Diabetes 32.5% % Hypertension 72% % ACEI 55%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear randomisation process, or if allocation concealment, unclear if missing data or exclusions post randomisation)

Overall Directness

Directly applicable

Briguori 2007

Bibliographic Reference	Briguori C; Airoldi F; D'Andrea D; Bonizzoni E; Morici N; Focaccio A; Michev I; Montorfano M; Carlino M; Cosgrave J; Ricciardelli B; Colombo A; Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies.; Circulation; 2007; vol. 115 (no. 10)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	2 secondary care centres.
Study dates	January 2005 - August 2006
Duration of follow-up	5 days

Inclusion criteria	Serum creatinine stable sCr concentration ≥176.8 µmol/l and/or glomerular filtration rate <40 mL · min -¹· 1.73 m-²
	Age at least 18 years of age
	Other Patients with CKD who underwent coronary and/or peripheral angiography and /or angioplasty
Exclusion criteria	Other conditions multiple myeloma, pulmonary edema, acute MI,
	Contrast recent exposure to radiographic contrast within 2 days of the study
	Medications administration of theophylline, dopamine, mannitol, or fenoldopam.
	History of dialysis
	Pregnancy or breastfeeding
	Serum creatinine sCr levels ≥8 mg/dL
Sample size	235
Loss to follow-up	16
Interventions	Contrast type iso-osmolar, nonionic
	Contrast name Iodixanol
	Contrast dose, ml, mean (SD) 320 mg iodine/mL
	Contrast procedure coronary and/or peripheral angiography and /or angioplasty
Outcome measures	Contrast induced AKI at 48 hours, defined as an increase in the sCr concentration ≥25% from the baseline value at 48 hrs after administration of the contrast
	Renal failure need for RRT

Study arms

NAC + sodium bicarbonate (N = 108)

Pre-procedure: NAc given orally at a dose of 1200mg twice daily, the day before and on the day of the procedure, with 154 mEq/L IV sodium bicarbonate (in dextrose and H2O) given at a dose of 3 ml/kg 1 hour pre-procedure. Post-procedure: Sodium bicarbonate given at a dose of 1 mL/kg/hour during procedure and or 6 hours after.

Sources of funding	none reported
% Female	19%
Mean age (SD)	70 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) Median 180.34 (IQR 166.94 - 208.62) umol/L % CKD 100% % Diabetes 49% % Hypertension 92% % ACEI 59%
Interventions	Contrast type iso-osmolar, nonionic Contrast name Iodixanol Contrast dose, ml, mean (SD) 169 (SD92) ml; 320 mg iodine/mL; Contrast procedure coronary and/or peripheral angiography and /or angioplasty

NAC + sodium chloride 0.9% (N = 111)

Pre-procedure: NAc given orally at a dose of 1200mg twice daily, the day before and on the day of the procedure, with 0.9% sodium chloride given at a dose of 1 mL/kg body weight/ hr (0.5 mL/kg for patients with left ventricular ejection fraction <40%) for 12 hours prior to procedure. Post-procedure: 0.9% sodium chloride (same dosing as pre-procedure) given for 12 hours.

% Female	24%

	Mean age (SD)	71 (SD9) years
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) Median (172.38 (IQR 149.40 - 199.78) umolL % CKD 100% % Diabetes 55% % Hypertension 86.5% % ACEI 58%
	Interventions	Contrast type iso-osmolar, nonionic Contrast name Iodixanol Contrast dose, ml, mean (SD) 179 (SD 102) ml; 320 mg iodine/mL Contrast procedure coronary and/or peripheral angiography and /or angioplasty

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear if allocation concealment, unclear reasons for missing data (>5% in either arm))

Overall Directness

Directly applicable

Caglar 2014

Bibliographic Reference	Caglar, I. M.; Caglar, F. N. T.; Conkbayir, C.; Baskurt, M.; Akturk, F.; Dasli, T.; Okcun, B.; Contrast study: Comparision of nephroprotective three protocols: Acetylcysteine-sodium bicarbonate-theophylline, to prevent contrast-induced nephropathy; Russian Journal of Cardiology; 2014; vol. 105 (no. 1); 27-31

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey;
Study setting	Single centre;
Study dates	Unclear
Duration of follow-up	48 hours for CIN, 2 years to assess major adverse events among people who developed CIN
Sources of funding	None reported;
Inclusion criteria	eGFR 30 to 60 ml/min/1.73m²
Exclusion criteria	Other conditions Acute coronary syndrome, cardiogenic shock, New York Heart Association class 3 - 4, > 4 Lown arrhythmia classification, hemodynamic instability Allergy Known allergy to NAC, theophylline, or contrast agents Contrast

	exposure within the prior 10 days Medications drugs that may interact with theophylline, or contraindications for theophylline Age <21 years Pregnancy or breastfeeding Pregnancy eGFR <30 and >60 ml/min/1.73m²
Outcome measures	Mortality Adverse events major adverse cardiac events Need for dialysis CIN An absolute 0.5 mg/ dL increase in SCr levels 48 hours after administration of radiocontrast medium was considered as CIN

Study arms

IV sodium bicarbonate (N = 50)

Sodium bicarbonate dose: 154 mL of 1000mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water. Volume: 3 ml/kg/h for 1 hour before the procedure, and 1 ml/kg/h during and for 6 hours after the procedure.

Sample size	50;
Loss to follow-up	None apparent
% Female	68
Mean age (SD)	68.3;± 10.2
Condition specific characteristics	% Diabetes 30 % Hypertension 64 Baseline serum creatinine, mg/dl, mean (SD) 1.33 ± 0.1

Interventions	Contrast type low osmolar, non-ionic iopromid Contrast name Ultravist Contrast dose, ml, mean (SD) 105.5 ± 56.3 Contrast procedure Coronary angiography

oral NAC + IV sodium bicarbonate (N = 50)

NAC dose: 600 mg p. o. twice daily. NAC given day before and day of coronary angiography. Sodium bicarbonate dose: sodium bicarbonate: 154 mL of 1000mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water. Sodium bicarbonate volume: 3 ml/kg/h for 1 hour before the procedure, 1 ml/kg/h during and for 6 hours after the procedure

Sample size	50;
Loss to follow-up	None apparent
% Female	28
Mean age (SD)	67.2;±;
Condition specific characteristics	% Diabetes 34 % Hypertension 60 Baseline serum creatinine, mg/dl, mean (SD) 1.36 ± 0.2
Interventions	Contrast type low osmolar, non-ionic iopromid Contrast name Ultravist Contrast dose, ml, mean (SD) 101.9 ± 46.3 Contrast procedure Coronary angiography

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(no clear protocol cited, unclear approach to missing data or if there was missing data, unclear if allocation concealment)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Carbonell 2007

Bibliographic Reference	Carbonell, Nieves; Blasco, Marisa; Sanjuán, Rafael; Pérez-Sancho, Esther; Sanchis, Juan; Insa, Luis; Bodí, Vicente; Núñez, Julio; García-Ramón, Rafael; Miguel, Alfonso; Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: A randomised trial; International Journal of Cardiology; 2007; vol. 115 (no. 1); 57-62

Study details

Study type	Randomised controlled trial (RCT)

Study location	Spain
Study setting	Tertiary care
Study dates	March 2002 - July 2005
Duration of follow-up	data collected until discharge of patient.
Sources of funding	none reported
Inclusion criteria	Other High risk coronary patients (diagnosed with angina at rest or post-MI or received thrombolytic therapy with failed recanalization so the cardiac catheterisation was an emergency procedure) with normal renal function (serum cr <123.8 umol/L or CrCl of >60 ml/min) undergoing coronary angiography
Exclusion criteria	Other conditions chronic renal failure, acute renal dysfunction, hemodynamic instability, untreated GI bleeding Allergy known allergy to NAC or contrast agents Medications previous treatment with theophylline, mannitol or nephrotoxic antibiotics
Sample size	216
Loss to follow-up	none reported
Interventions	Contrast type non-ionic low osmolar Contrast name iopromide Contrast dose, ml, mean (SD) 370 mg iodine/ml Contrast procedure coronary angiography
Outcome measures	Contrast induced AKI at 48 hours, defined at acute increase in serum Cr of at least 25% or 44umol/L over baseline. Mortality during hospital stay

Study arms

IV NAC + IV sodium chloride 0.45% (N = 107)

Pre-procedure: 600mg IV NAC diluted in 50ml of 0.9% saline, given for 30 mins, twice daily, starting within 6 hours before procedure, with 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

% Female	19.6%
Mean age (SD)	63.1 (SD 13.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 83.10 (SD14.14) % Diabetes 27.5% % Hypertension 52.3% % ACEI 62.6% % NSAIDs 89.7%

IV sodium chloride 0.45% (N = 109)

Pre-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

% Female	27.5%
Mean age (SD)	60.7 (SD11.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 84.86 (SD 15.03) umol/L % Diabetes 27.5% % Hypertension 57.8% % ACEI 53.3%

		% NSAIDs 83.5%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Carbonell 2010

Bibliographic Reference	Carbonell N; Sanjuán R; Blasco M; Jordá A; Miguel A; N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients.; Revista espanola de cardiologia; 2010; vol. 63 (no. 1)

Study details

Study type	Randomised controlled trial (RCT)

	Associated study of another trial Chronic renal disease subgroup study of Carbonell 2007
Study location	Spain
Study setting	Tertiary care
Study dates	March 2002- December 2006
Duration of follow-up	1 year
Sources of funding	none reported
Inclusion criteria	Serum creatinine chronic renal disease, defined as stable serum Cr ≥123.76 umol/L or <60ml/min CrCl Other same as associated study (see Carbonell 2007 for full list of inclusion and exclusion criteria)
Sample size	81
Loss to follow-up	0
Interventions	Contrast type non-ionic low osmolar Contrast name Iopromide Contrast dose, ml, mean (SD) 370 mg iodine/ml Contrast procedure Coronary angiography
Outcome measures	Contrast induced AKI at 48 hours, defined at acute increase in serum Cr of at least 25% or 44umol/L over baseline. Mortality Length of hospital stay Renal failure Need for RRT

Study arms

IV NAC + 0.45 sodium chloride (N = 39)

Pre-procedure: 600mg IV NAC diluted in 50ml of 0.9% saline, given for 30 mins, twice daily, starting within 6 hours before procedure, with 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

Study type	Associated study of another trial Chronic renal disease subgroup study of Carbonell 2007
% Female	20.5%
Mean age (SD)	69 (SD11) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 177.68 (SD 68.07) umol/L % CKD 100% % Diabetes 43% % ACEI 38% % NSAIDs 69%

0.45% sodium chloride (N = 42)

Pre-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour 6 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1 ml/kg/hour for 12 hours.

Study type	Associated study of another trial Chronic renal disease subgroup study of Carbonell 2007
% Female	19.1%
Mean age (SD)	165.31 (SD 61.88)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 165.31 (SD 61.88) % CKD 100%

		% Diabetes 51% % Hypertension 71% % ACEI 36% % NSAIDs 64%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Castini 2010

Bibliographic Reference	Castini, Diego; Lucreziotti, Stefano; Bosotti, Laura; Salerno Uriarte, Diego; Sponzilli, Carlo; Verzoni, Alessandro; Lombardi, Federico; Prevention of Contrast-induced Nephropathy: A Single Center Randomized Study; Clinical Cardiology; 2010; vol. 33 (no. 3); e63-e68

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	single centre, cardiology unit
Duration of follow-up	5 days
Sources of funding	none reported
Inclusion criteria	Serum creatinine stable serum creatinine levels ≥ 106µmol/l Age at least 18 years of age Other undergoing non-emergency coronary angiography or PCI
Exclusion criteria	Other conditions multiple myeloma, pulmonary oedema, cardiogenic shock or acute MI; “previous enrolment in same or other protocols” Allergy allergy to contrast or NAC Contrast exposure to contrast in last 7 days Medications administration of theophylline, mannitol, dopamine, dobutamine, NSAIDs or fenoldopam History of dialysis history of RRT Pregnancy or breastfeeding Procedures need for emergency cardiac catheterisation
Sample size	156
Loss to follow-up	0

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 132 (SD27) umol/L % CKD 100% % Diabetes 26.4% % Hypertension 83% % ACEI 75.5%
Interventions	Contrast type iso-osmolar Contrast name iodixanol Contrast procedure non-emergency coronary angiography or PCI Intervention (more details) All groups: “home therapy” continued for entire length of protocol except metformin which was stopped 24h pre-procedure and reintroduced after 5 days if CI-AKI did not occur.
Outcome measures	Contrast induced AKI at 5 days: defined as an increase in sCr ≥25% baseline, reported separately using the definition of an absolute increase in sCr ≥44.2 µmol/l Renal failure need for RRT

Study arms

	oral NAC + sodium chloride 0.9% (N = 53) pre-procedure: 600mg NAC Twice daily on day before and day of administration of contrast, IV sodium chloride at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: same dose as pre-procedure, for 12 hours.

% Female	5.7%
Mean age (SD)	70.5 (SD 7.2) years
Interventions	Contrast type iso-osmolar

	Contrast name iodixanol Contrast dose, ml, mean (SD) 210 (SD 140.6) ml Contrast procedure non-emergency coronary angiography or PCI

Sodium chloride 0.9% (N = 52)

pre-procedure: IV sodium chloride at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: same dose as pre-procedure, for 12 hours.

% Female	15.7%
Mean age (SD)	72.7 (SD 8.2) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 139 (SD 34) umol/L % CKD 100% % Diabetes 19.6% % Hypertension 78.4% % ACEI 72.5%
Interventions	Contrast type iso-osmolar Contrast name iodixanol Contrast dose, ml, mean (SD) 196.4 (SD 127.7) ml Contrast procedure non-emergency coronary angiography or PCI

Sodium bicarbonate (N = 52)

	pre-procedure: IV sodium bicarbonate 154ml of 100mEq/L in 846ml of 5% dextrose in H2O, at 3ml/kg for 1 hour immediately before contrast. Post-procedure: IV sodium bicarbonate at 1ml/kg/hour for 6 hours.
% Female	15.4%
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 141 (SD 34) umol/L % CKD 100% % Diabetes 34.6% % Hypertension 71.2% % ACEI 69.2%
Interventions	Contrast type iso-osmolar Contrast name iodixanol Contrast dose, ml, mean (SD) 179.2 (SD 125.1) ml Contrast procedure non-emergency coronary angiography or PCI

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(however unclear if allocation concealment)

Overall Directness

Directly applicable

Chen 2008

Bibliographic Reference	Chen, Shao Liang; Zhang, Junjie; Yei, Fei; Zhu, Zhongsheng; Liu, Zhizhong; Lin, Song; Chu, Jun; Yan, Ji; Zhang, Ruiyan; Kwan, Tak W.; Clinical outcomes of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention: a prospective, multicenter, randomized study to analyze the effect of hydration and acetylcysteine; International journal of cardiology; 2008; vol. 126 (no. 3); 407-13

Study details

Study location	China
Study setting	3 centres in China
Duration of follow-up	up to 6 months
Sources of funding	none reported
Inclusion criteria	Other people with myocardial ischemia (angina or positive exercise treadmill) scheduled for elective PCI
Exclusion criteria	Other conditions Chronic peritoneal or haemodialysis; acute MI on admission Procedures

	coronary anatomy that makes them unsuitable for PCI, or if emergency CABG is required
Sample size	936
Loss to follow-up	none reported
Interventions	Contrast type Iso-osmolar Contrast name not reported Contrast procedure PCI
Outcome measures	Contrast induced AKI at 48 hours, defined as an increase in sCr of over 44.2 umol/L Mortality at 6 months Renal failure need for RRT; haemofiltration performed if oligoanuria >48h despite administration of furosemide >1g iv per 24h

Study arms

	<sCr of 132.6 umol/L: Sodium chloride 0.45% (N = 330) Pre-procedure: 0.45% sodium chloride given at a dose of 1ml/kg/hour 12 hours before angiogram. Post-procedure: sodium chloride 0.45% given at a dose of 1ml/kg/hour for 6 hours. Patient characteristics were not reported per arm. **<sCr of 132.6 umol/L: non-hydration (N = 330)** Pre-procedure: non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Post-procedure: non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Patient characteristics were not reported per arm. **≥sCr of 132.6 umol/L: NAC + sodium chloride 0.45% (N = 188)** Pre-procedure: NAC given twice orally loading dose of 1200mg, with 0.45% sodium chloride given at a dose of 1ml/kg/hour, both 12 hours before angiogram. Post-procedure: NAC given immediately after angiogram, with sodium chloride 0.45%

	given at a dose of 1ml/kg/hour for 6 hours. Patient characteristics were not reported per arm. **≥sCr of 132.6 umol/L: NAC + non-hydration (N = 188)** Pre-procedure: NAC given twice orally loading dose of 1200mg, with non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Post-procedure: NAC given immediately after angiogram, with non-hydration (protocol for non-hydration not fully described, unclear if oral fluids allowed and if so how much). Patient characteristics were not reported per arm.

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(This study provided a lack of information regarding the randomisation process and allocation concealment. In addition, it did not report baseline characteristics across trial arms. Lastly, study does not describe missing data or exclusions post-randomisation, it is likely that there were many since the sample size was so large.)

Overall Directness
Directly applicable.

Cho 2010

Bibliographic Reference	Cho R; Javed N; Traub D; Kodali S; Atem F; Srinivasan V; Oral hydration and alkalinization is noninferior to intravenous therapy for prevention of contrast-induced nephropathy in patients with chronic kidney disease.; Journal of interventional cardiology; 2010; vol. 23 (no. 5); 460-466

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Single hospital centre
Study dates	February;2005 to February;2010
Duration of follow-up	72 hours for CIN, but length of hospital stay and inpatient mortality was also collected.;
Sources of funding	None described
Inclusion criteria	Serum creatinine stable serum creatinine levels of at least 1.1 mg/dL or estimated creatinine clearance less than 60 mL/min Age 18 years or older received imaging undergoing diagnostic, elective coronary angiogram Chronic kidney disease
Exclusion criteria	Other conditions multiple myeloma or other myeloproliferative disease; current decompensated heart failure or significant change in baseline New York Heart Association Class; current myocardial infarction; symptomatic hypokalemia; uncontrolled hypertension; exacerbation of chronic obstructive pulmonary disease Allergy allergy to radiographic contrast, Contrast exposure to radiocontrast within 7 days of enrollment

	Medications administration of dopamine, mannitol, fenoldapam, or NAC during the time of the study History of dialysis Pregnancy or breastfeeding Pregnancy Blood pressure uncontrolled hypertension (treated systolic blood pressure >200 mmHg or diastolic blood pressure>100 mmHg) Procedures emergency catheterization Serum creatinine serum creatinine levels greater than 8.0 mg/dL; change in serum creatinine levels of at least 0.5 mg/dL during the previous 24 hours other serum bicarbonate greater than 28 mEq/L, and sodium less than 133 mEq/L
Sample size	91
Loss to follow-up	None reported
Interventions	Contrast type nonionic, low-osmolarity Contrast name isoversol Contrast procedure Elective diagnostic coronary angiography
Outcome measures	Mortality in-hospital mortality Length of hospital stay CIN greater than 25% increase in serum creatinine from baseline or an absolute increase of 0.5 mg/dL from baseline at 72 hours following exposure to radiocontrast

Study arms

	IV sodium chloride 0.9% (N = 27) IV sodium chloride: 154 mEq/L. 3 mL/kg for 1 h pre-contrast and 1 mL/kg for 6 h post contrast

% Female	37.1
Mean age (SD)	77.33 (8.39)
Condition specific characteristics	% Diabetes 29.6 % Hypertension 100 % ACEI ACEi or ARB: 81.5% % NSAIDs Aspirin: 96.3% Baseline serum creatinine, mg/dl, mean (SD) 1.38 (no standard deviation reported)
Interventions	Contrast dose, ml, mean (SD) 122.59 (no standard deviation reported)

IV sodium bicarbonate (N = 21)

IV sodium bicarbonate: 154 mEq/L. 3 mL/kg for 1 h pre-contrast and 1 mL/kg for 6 h post-contrast

% Female	47.6
Mean age (SD)	78.47 (8.72)
Condition specific characteristics	% Diabetes 42.9 % Hypertension 90.5 % ACEI ACEi or ARB: 81.0 % NSAIDs Aspirin: 95.2% Baseline serum creatinine, mg/dl, mean (SD) 1.41 (no SD reported)
Interventions	Contrast dose, ml, mean (SD) 136.31 (no SD reported)

oral hydration with water (N = 22)

500 mL of water 4 h prior to contrast exposure and stopped 2 h prior to procedure. Then 600 mL of water post procedure.

% Female	55.6
Condition specific characteristics	% Diabetes 36.4 % Hypertension 95.5 % ACEI ACEi or ARB: 59.1% % NSAIDs Aspirin: 90.9% Baseline serum creatinine, mg/dl, mean (SD) 1.38 (no SD reported)
Interventions	Contrast dose, ml, mean (SD) 118.57 (no SD reported)

oral hydration with water + oral sodium bicarbonate (N = 21)

500 mL of water 4 h prior to procedure and stopped 2 h prior to contrast exposure oral sodium bicarbonate: 3.9 g (46.4 mEq) 20 min prior to contrast exposure. Then 600 mL of water and 1.95 g (30.4 mEq) of oral sodium bicarbonate 2 hours and 4 hours after the contrast exposure.

% Female	61.9
Mean age (SD)	79.10 (1.83)
Condition specific characteristics	% Diabetes 47.6 % Hypertension 95.2 % ACEI ACEi or ARB: 57.1 % NSAIDs Aspirin: 100 Baseline serum creatinine, mg/dl, mean (SD)

		1.31 (no SD reported)
	Interventions	Contrast dose, ml, mean (SD) 136.5 (no SD reported)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(ial terminated early and unclear stopping rules, although interim analysis was planned. Also insufficient information about randomisation process and allocation concealment.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Chong 2015

Bibliographic Reference	Chong, E.; Poh, K. K.; Lu, Q.; Zhang, J. J. J.; Tan, N.; Hou, X. M.; Ong, H. Y.; Azan, A.; Chen, S. L.; Chen, J. Y.; Ali, R. M.; Fang, W. Y.; Lau, T. W. L.; Tan, H. C.; Comparison of combination therapy of high-dose oral N-acetylcysteine and

intravenous sodium bicarbonate hydration with individual therapies in the reduction of Contrast-induced Nephropathy during Cardiac Catheterisation and Percutaneous Coronary Intervention (CONTRAST): A multi-centre, randomised, controlled trial; International Journal of Cardiology; 2015; vol. 201; 237-242

Study details

Study type	Randomised controlled trial (RCT)
Study location	Singapore
Study setting	Multi-centre
Study dates	August 2007 - May 2013
Duration of follow-up	30 days
Sources of funding	None reported however study states no relationship with industry
Inclusion criteria	Age >21 years eGFR 15 - 60 ml/min/1.73m² Other scheduled to receive elective cardiac catheterisation with or without PCI, and able to receive pre-hydration for 12 hours
Exclusion criteria	Other conditions Pulmonary oedema, moderate to severe congestive heart failure, inability to withstand fluid load and presence of haemodynamic compromise, uncontrolled hypertension, severe sepsis, Allergy to contrast or NAC Contrast exposure to contrast in the prior two days Medications use of renal-toxic drugs such as NSAIDs, aminoglycoside, cyclosporin, and cisplatin within 48 hours of catheterisation; administration of sodium bicarbonate or NAC within 48 hours of cardiac catheterisation History of dialysis Related conditions Acute kidney failure with >44 µmol/L increase in serum Cr in the previous 24 hours Blood pressure systolic > 150 mm Hg or diastolic >100 mm Hg

	Procedures Emergency cardiac catheterisation eGFR <15 ml/min/1.73m²
Sample size	548
Loss to follow-up	82
Interventions	Contrast type non-ionic, low osmolarity Contrast name ohexol, iopamidol, ioversol and iopromide Contrast procedure Cardiac catheterisation with or without PCI
Outcome measures	Mortality 30 day mortality Length of hospital stay Need for dialysis CIN ≥25% increase of serum Cr concentration or a ≥44 µmol/L (0.5mg/dL) increase in serum Cr within 48 h of cardiac catheterisation or PCI

Study arms

	high-dose oral NAC + IV sodium chloride 0.9% (N = 185) NAC: 2 tablets of 600 mg dissolved in approximately 250 mL of water. Twice a day for 3 consecutive days, starting from the day before cardiac catheterisation (to a total of 6 doses). Sodium chloride 0.9%: 154 mEq/L at a rate of 1mL/kg/h, for 12 h pre contrast and 6 hours post contrast.

Sample size	185
Loss to follow-up	28
% Female	28
Mean age (SD)	69.0

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 134.0 (35.5) % CKD 52.9 % Diabetes 49.7 % Hypertension 90.5
Interventions	Contrast dose, ml, mean (SD) 116 (83.5)

abbreviated IV sodium bicarbonate (N = 182)

abbreviated loading IV infusion of 154 mEq/L sodium bicarbonate in 5% dextrose solution: 3 mL/kg/h for 1 h before cardiac catheterisation, and 1 mL/kg/h during and until 6 h post-contrast

Sample size	182
Loss to follow-up	29
% Female	22.2
Mean age (SD)	68.4 (10.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 47.3 (14.1) % CKD 55.6 % Diabetes 45.1 % Hypertension 85.0
Interventions	Contrast dose, ml, mean (SD) 115 (85.4)

high-dose oral NAC + abbreviated IV sodium bicarbonate (N = 181)

	1.2 g oral NAC and abbreviated loading IV infusion of 154 mEq/L sodium bicarbonate in 5% dextrose solution: 3 mL/kg/h for 12 h before cardiac catheterisation, and 1 mL/kg/h during and until 6 h post-contrast

Sample size	181
Loss to follow-up	25
% Female	22.4
Mean age (SD)	67.0 (10.2)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 138.7 (36.6) % CKD 53.9 % Diabetes 48.1 % Hypertension 89.1
Interventions	Contrast dose, ml, mean (SD) 116 (84.5)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(significant protocol deviations; unclear statistical approach; large amount of exclusions and open label)

Overall Directness

Directly applicable

Durham 2002

Bibliographic Reference	Durham JD; Caputo C; Dokko J; Zaharakis T; Pahlavan M; Keltz J; Dutka P; Marzo K; Maesaka JK; Fishbane S; A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography.; Kidney international; 2002; vol. 62 (no. 6)

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	inpatient centre
Study dates	December 2000 - November 2001
Duration of follow-up	48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine baseline serum Cr >1.7mg/dL Age at least 18 years of age Other referred for cardiac angiography (diagnostic or therapeutic procedures)

Exclusion criteria	Other conditions renal disease determined to have a reversible component; evidence of active atheroembolic disease, severe asthma, severe peptic ulcer disease, respiratory depression Allergy known prior insensitivity to acetycsteine, Pregnancy or breastfeeding or women of child bearing potential not using an approved contraceptive method. Procedures inadequate time prior to angiography to perform procedures for the study Serum creatinine measurements varied by more than 15% in the 3 days prior to angiography. Unable to comply with follow-up
Sample size	81
Loss to follow-up	2
Interventions	Contrast type low osmolar non-ionic Contrast name omnipaque (iohexel) Contrast dose, ml, mean (SD) rate and duration of contrast at discretion of physician Contrast procedure angiography
Outcome measures	Contrast induced AKI at 48 hours, defined as an incrase in serum Cr of 0.5mg/dl

Study arms

	Oral NAC + IV sodium chloride 0.45% (N = 38) Pre-procedure: 1200mg (2400mg total) dose of NAC (mixed with 6ml orange juice) 1 hour precontrast, with 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for 12 hours before procedure. Post-procedure: remaining NAC given over 3 hours, with 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for up to 12 hours.

% Female	36.8%

Mean age (SD)	71.4 (SD 12.2) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 194.48 (SD 32.36) umol/L % Diabetes 50% % Hypertension 57%

IV sodium chloride 0.45% (N = 41)

Pre-procedure: 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for 12 hours before procedure. Post-procedure: 0.45% sodium chloride given at a dose of 1.0ml/kg/hour for up to 12 hours.

% Female	31.7%
Mean age (SD)	69.8 (SD 9.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 203.32 (SD 44.2) umol/L % Diabetes 46.3% % Hypertension 64.4%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Erturk 2014

Bibliographic Reference	Erturk, Mehmet; Uslu, Nevzat; Gorgulu, Sevket; Akbay, Ertan; Kurtulus, Gulsah; Akturk, Ibrahim F.; Akgul, Ozgur; Surgit, Ozgur; Uzun, Fatih; Gul, Mehmet; Isiksacan, Nilgun; Yildirim, Aydin; Does intravenous or oral high-dose N-acetylcysteine in addition to saline prevent contrast-induced nephropathy assessed by cystatin C?; Coronary artery disease; 2014; vol. 25 (no. 2); 111-7

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey;
Study setting	Single-centre
Study dates	November 2010 to April 2012
Duration of follow-up	1 year
Sources of funding	None described
Inclusion criteria	Age eGFR < 60 ml/min/1.73 m²

Exclusion criteria	Other conditions Uncontrolled hypertension; acute and chronic inflammatory disease; Allergy known allergy to contrast agents and NAC Contrast Exposure within 7 days Medications Medication with NSAID or metformin up to 2 days before entering the study; patients receiving fenoldopam, mannitol, dopamine, and theophylline History of dialysis Pregnancy or breastfeeding Pregnancy Blood pressure >160 mmHg systolic and >110 mmHg diastolic, respectively eGFR <15 ml/min/1.73 m²
Sample size	315
Loss to follow-up	8
% Female	36.5
Mean age (SD)	66 (9)
Interventions	Contrast type nonionic, low-osmolarity Contrast name Ultravist Contrast dose, ml, mean (SD) 125 (74) Contrast procedure Intra-arterial procedure: PCI, coronary angiography with or without PCI, "peripheral procedures", "others"
Outcome measures	Mortality deaths and cardiovascular deaths at 30 days and 1 year Need for dialysis at 30 days and 1 year CIN an increase in the SCr or cystatin C concentration of at least 0.5mg/dl and/or at least 25% from the baseline value at 48 h after administration of the contrast dye; AND

	increase in the SCr or cystatin C concentration of at least 0.3 mg/dl from the baseline value at 48 h after administration of the contrast dye; AND ncrease in the serum cystatin C concentration of at least 10% from the baseline value at 48 h after administration of the contrast dye. Definitions reported separately. Composite outcome Death, cardiovascular death, and need for dialysis at 30 days and at 1 year

Study arms

IV sodium chloride 0.9% (N = 105)

Administered a rate of 1ml/kg/h for 12 h before and 12 h after the procedure

Sample size	105
Loss to follow-up	3
% Female	36.9
Mean age (SD)	65;(8)
Condition specific characteristics	% CKD eGFR 15 - 29: 10.7% eGFR 30 - 59: 89.3% % Diabetes 52.4 % Hypertension 84.5 % ACEI 38.8 Baseline serum creatinine, mg/dl, mean (SD) 1.52 (0.47)
Interventions	Contrast dose, ml, mean (SD) 127 (66)

oral NAC + IV sodium chloride 0.9% (N = 105)

oral NAC: 1200 mg sachet every 12 h for 24 h before and 48 hours after procedure (a total of 3 days and a total dose of NAC, 7200mg) IV sodium chloride 0.9%: 1ml/kg/h for 12 h before and after the procedure

Sample size	1

Loss to follow-up	3
% Female	3
Mean age (SD)	65;(8)
Condition specific characteristics	% CKD eGFR 15 - 29: 6.9%, eGFR 30 - 59: 93.1% % Diabetes 49 % Hypertension 76.5 % ACEI 44.1 Baseline serum creatinine, mg/dl, mean (SD) 1.46 (0.36)
Interventions	Contrast dose, ml, mean (SD) 127 (89)

IV NAC + IV sodium chloride 0.9% (N = 105)

IV NAC: a dose of 2400mg within 1 h immediately before the procedure and followed by 4800mg within 4–6 h after the procedure (a total dose of NAC, 7200mg). IV sodium chloride 0.9%: 1ml/kg/h for 12 h before and after the procedure

Sample size	105
Loss to follow-up	3
% Female	35.3
Condition specific characteristics	% CKD eGFR 15 - 29: 4.9% eGFR 30 - 59: 95.1% % Diabetes 49 % Hypertension 88.2 % ACEI 34.3

		Baseline serum creatinine, mg/dl, mean (SD) 1.49 (0.39)
	Interventions	Contrast dose, ml, mean (SD) 122 (67)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Ferrario 2009

Bibliographic Reference	Ferrario, Francesca; Barone, Maria Teresa; Landoni, Giovanni; Genderini, Augusto; Heidemperger, Marco; Trezzi, Matteo; Piccaluga, Emanuela; Danna, Paolo; Scorza, Daniele; Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy?a randomized controlled study; ndt; 2009; vol. 24 (no. 10); 3103-3107

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	University hospital
Study dates	Between March 2003 and January 2005
Duration of follow-up	Baseline to the maximum value. Plasmatic creatinine was assayed by the hospital laboratory during the preprocedural period, and daily for 3 days after the procedure.
Sources of funding	Not reported
Inclusion criteria	Age 18 years or older Other creatinine clearance <55 ml/min; scheduled for elective coronary and/or peripheral angiography and/or angioplasty and had a stable renal function as documented by a small ±10% variation in serum creatinine pre-procedural values when compared to the outpatients values performed 3–30 days before the procedure
Exclusion criteria	Other conditions New York Health Association status III to IV, ongoing acute myocardial infarction or acute coronary syndrome Allergy to NAC Medications need for theophylline, dopamine, fenoldopam, mannitol or nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, fluoroquinolones, aminoglycosides . . .) within 1 week of the procedure other renal replacement therapy, the presence of clinical signs of dehydration and systemic hypotension
Sample size	200
Interventions	Contrast type isosmolar, non-ionic, dimeric Contrast name Iodixanolo, Visipaque Contrast procedure elective diagnostic and interventional angiography

	Intervention (more details) Oral clear fluid intake was not restricted before or after the procedure
Outcome measures	Contrast induced AKI increase of serum creatinine levels of 25% or more and/or 0.5 mg/dl or more Notes No patient required renal replacement therapy and no patient died in hospital

Study arms

oral NAC + IV sodium chloride 0.9% (N = 99)

Pre-contrast: oral NAC twice daily the day before the procedure, with IV sodium chloride 0.9% 1 ml/kg/h 12-24 h. Post-contrast: oral NAC twice daily the day of the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 24 h.

Loss to follow-up	None
% Female	32
Mean age (SD)	75 (7.7)
Condition specific characteristics	% Diabetes 25 % Hypertension 80 % ACEI 49
Interventions	Contrast dose, ml, mean (SD) 180 (104.4)

IV sodium chloride 0.9% (N = 101)

Pre-contrast: placebo (tablets containing glucose) the day before the procedure, with IV sodium chloride 0.9% 1 ml/kg/h 12-24 h. Post-contrast: placebo (tablets containing glucose) the day of the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 24 h.

Loss to follow-up	None
% Female	38

	Mean age (SD)	75 (6.9)
	Condition specific characteristics	% Diabetes 25 % Hypertension 83 % ACEI 52
	Interventions	Contrast dose, ml, mean (SD) 168 (103.3)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if assessor was blinded; no protocol cited)

Overall Directness

Directly applicable

Fung 2004

Bibliographic Reference	Fung JW; Szeto CC; Chan WW; Kum LC; Chan AK; Wong JT; Wu EB; Yip GW; Chan JY; Yu CM; Woo KS; Sanderson JE; Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 2004; vol. 43 (no. 5)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Hong Kong
Study setting	Cardiology department, university hospital
Duration of follow-up	48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine sCr 149 - 400µmol/l; 2 sCr measurements within one month of angiography with <15% change to confirm stable renal function Other undergoing elective coronary angiography or PCI
Exclusion criteria	Other conditions Cardiogenic shock Allergy Known allergy to NAC or contrast agents Medications Concomitant use of dopamine, theophylline or mannitol History of dialysis Current RRT
Sample size	91
Loss to follow-up	0
Interventions	Contrast type

	low osmolar Contrast name iopromide Contrast procedure coronary angiography or PCI
Outcome measures	Contrast induced AKI at 48 hours, increase in sCr ≥ 44µmol/l or reduction in GFR ≥25%); subgroup analysis given for patients with diabetes Adverse events including allergic reaction, not including heart failure; clinical heart failure so could not complete sodium chloride infusion regimen Renal failure Need for RRT

Study arms

NAC + sodium chloride (N = 46)

Pre-procedure: 400mg on the day before and day of procedure. IV sodium chloride 0.9% 100ml/hour for 12 hours Post-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours

% Female	26.1%
Mean age (SD)	68.2 (SD 8.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 201 (SD 48) umol/L % CKD 100% % Diabetes 50% % ACEI 50% ACEI/ARB % NSAIDs 84.8%
Interventions	Contrast type low osmolar Contrast name iopromide

	Contrast dose, ml, mean (SD) 135.8 (SD 66.6) ml Contrast procedure coronary angiography or PCI

Sodium chloride 0.9% (N = 45)

Pre-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours Post-procedure: IV sodium chloride 0.9% 100ml/hour for 12 hours

% Female	33.3%
Mean age (SD)	68.0 (SD 8.8)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 210 (SD 54) umol/L % CKD 100% % Diabetes 55.6% % ACEI 57.8% ACEI or ARB % NSAIDs 71.1%
Interventions	Contrast type low osmolar Contrast name iopromide Contrast dose, ml, mean (SD) 121.0 (SD 66.2) ml Contrast procedure coronary angiography or PCI

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Goldenberg 2004

Bibliographic Reference	Goldenberg I; Shechter M; Matetzky S; Jonas M; Adam M; Pres H; Elian D; Agranat O; Schwammenthal E; Guetta V; Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature.; European heart journal; 2004; vol. 25 (no. 3)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Tertiary care
Study dates	March 2001 - October 2002
Duration of follow-up	up to 6 months (for mortality outcomes);

Sources of funding	none reported
Inclusion criteria	Serum creatinine calculated CrCl of <50ml/min (if person is without diabetes) or <100ml/min (if person has diabetes); any patient with an absolute serum creatinine of >200 umol/L received imaging previous diagnostic angiography undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI
Exclusion criteria	Other conditions reactive airway disease requiring oral steroids; active congestive heart failure, acute MI Medications ongoing need for IV nitroglycerine and treatment with NAC within 72 hours of PCI History of dialysis RRT (dialysis or transplantation) Pregnancy or breastfeeding women of child-bearing age Blood pressure systolic BP <80 mmHg Procedures enrollment in another clinical trial Unable to comply with follow-up
Sample size	180
Loss to follow-up	34 (25 in hospital phase and additional 9 into the long term follow up)
Interventions	Contrast type low osmolar nonionic Contrast name Omnipaque Contrast dose, ml, mean (SD) not reported Contrast procedure PCI or urgent coronary angiography in people with high likelihood of ad hoc PCI
Outcome measures	Contrast induced AKI At 48 hours, incidence of CIN: defined as increase in serum creatinine of at least 25% Mortality in-hospital and at 6 months Renal failure

	need for RRT)in hospital and at 6 months)

Study arms

Oral NAC + IV sodium chloride 0.45% (N = 95)

Pre-procedure: first dose given 8pm night before procedure with subsequent doses at 8am and 8pm day of procedure (to a total dose of 6000mg). Alternatively, participants received the first dose at 8am and 8pm on the day of the procedure(to a total dose of 4000mg). IV 0.45% sodium chloride was given at a dose of 75ml/hour for 24 hours beginning at the time of enrollment.

% Female	32%
Mean age (SD)	71 (SD 8) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 124 (SD 49) umol/L % Diabetes 68% % Hypertension 72%

IV sodium chloride 0.45% (N = 85)

IV 0.45% sodium chloride was given at a dose of 75ml/hour for 24 hours beginning at the time of enrollment.

% Female	34%
Mean age (SD)	69 (SD 11) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) % Diabetes 67% % Hypertension 77%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Gomes 2005

Bibliographic Reference	Gomes, V O; Poli de Figueredo, C E; Caramori, P; Lasevitch, R; Bodanese, L C; Ara?jo, A; R?edel, A P; Caramori, A P; Brito, F S; Bezerra, H G; Nery, P; Brizolara, A; N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial; Heart; 2005; vol. 91 (no. 6); 774

Study details

Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Hospital
Study dates	From April 2001 to April 2003

Duration of follow-up	48h
Sources of funding	Not reported
Inclusion criteria	Other at risk for developing CI-AKI if participants had one of the following criteria: serum creatinine ≥106.08 mmol/l, creatinine clearance <50 ml/min, or drug treated diabetes mellitus
Exclusion criteria	Contrast use of radiographic contrast media within 21 days of randomisation Age under 18 years History of dialysis current dialysis other haemodynamic instability before the procedure (systolic blood pressure ≤90 mm Hg or diastolic blood pressure ≤60 mm Hg), history of sensitivity to N-acetylcysteine
Sample size	156
Interventions	Contrast type low osmolality, ionic Contrast name ioxaglate (Hexabrix) Contrast procedure elective CAG or PCI
Outcome measures	Contrast induced AKI increase in serum creatinine ≥44.2 mmol/l Mortality In-hospital death Number of patients needing RRT Need for haemodialysis Length of hospital stay Reported as centiles

Study arms

	oral NAC + IV sodium chloride 0.9% (N = 77)

Pre-contrast: oral NAC 600 mg orally twice a day 1 day before procedure (2 doses), with IV sodium chloride 0.9% 1 mL/kg/min 12 h before contrast. Post-contrast: oral NAC 600 mg orally twice a day 2 doses after the procedure, with IV sodium chloride 0.9% 1 ml/kg/h for 12 h after contrast.

Loss to follow-up	None
% Female	39.0
Mean age (SD)	63.8 (11.30)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 123.76 (45.08) % Diabetes 51.9 % Hypertension 87.0 % ACEI 70.1
Interventions	Contrast dose, ml, mean (SD) 102.5 (47.3)

IV sodium chloride 0.9% (N = 79)

Pre-contrast: matching placebo, with IV sodium chloride 0.9% 1 mL/kg/min 12 h before contrast. Post-contrast: matching placebo, with IV sodium chloride 0.9% 1 ml/kg/h for 12 h after contrast.

Loss to follow-up	None
% Female	43.0
Mean age (SD)	66.5 (11.1)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 111.38 (30.94) % Diabetes 51.9 % Hypertension

		84.8 % ACEI 68.4
	Interventions	Contrast dose, ml, mean (SD) 102.8 (60.4)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if assessor was blinded; no protocol cited)

Overall Directness

Directly applicable

Habib 2016

Bibliographic Reference	Habib, Mohammed; Hillis, Alaa; Hammad, Amen; N-acetylcysteine and/or ascorbic acid versus placebo to prevent contrast-induced nephropathy in patients undergoing elective cardiac catheterization: The NAPCIN trial; A single-center, prospective, randomized trial; Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia; 2016; vol. 27 (no. 1); 55-61

Study details

Study type	Randomised controlled trial (RCT)
Study location	Palestine
Study setting	Single hospital centre
Study dates	None reported
Duration of follow-up	48 hours
Sources of funding	None declared
Inclusion criteria	received imaging undergoing coronary angiography Moderate to high CIN risk at least one risk factor for CIN: age >70 years, baseline creatinine level >1.5 mg/dL, heart failure, diabetes mellitus or contrast media volume >300 mL Other Ischaemic heart disease or peripheral vascular disease
Sample size	105
Loss to follow-up	None reported
% Female	41.9
Mean age (SD)	62.3 (8.9)
Interventions	Contrast type low-osmolar, non-ionic Contrast name iopromide (Ultravist) Contrast dose, ml, mean (SD) not reported

	Contrast procedure Coronary angiography and/or PCI
Outcome measures	CIN an increase in serum creatinine concentration of 0.5 mg/dL or ≥25% of the baseline value within 48 h after the procedure

Study arms

oral NAC + IV sodium chloride 0.9% (N = 30)

NAC: 1200 mg orally every 12 h over 48 hours, one dose before coronary angiography and three doses after coronary angiography (total dose of NAC, 4800 mg including intervention dose); 0.9% saline: started just before injection of contrast media and continued for 12 h at a rate 1.0 mL/kg/min after angiography

Sample size	30
% Female	33.4
Mean age (SD)	63.
Condition specific characteristics	% Diabetes not reported for this arm Baseline serum creatinine, mg/dl, mean (SD) 1.09 (0.45)
Interventions	Contrast dose, ml, mean (SD) not reported

IV sodium chloride 0.9% (N = 45)

0.9% saline: started just before injection of contrast media and continued for 12 h at a rate of 1.0 mL/kg/min after angiography

Sample size	45
% Female	not reported for this arm
Mean age (SD)	63 (8.26)

	Condition specific characteristics	% Diabetes 75.5 Baseline serum creatinine, mg/dl, mean (SD) 79.78 (18.53)
	Interventions	Contrast dose, ml, mean (SD) 13 patients received >300ml of contrast media

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

High

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

(not enough information about how analysis was performed and whether all randomised participants were included)

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

(Study did not report missing outcome data)

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Hafiz 2012

Bibliographic Reference	Hafiz, Abdul Moiz; Jan, M. Fuad; Mori, Naoyo; Shaikh, Fareed; Wallach, Jeffrey; Bajwa, Tanvir; Allaqaband, Suhail; Prevention of contrast-induced acute kidney injury in patients with stable chronic renal disease undergoing elective percutaneous coronary and peripheral interventions: randomized comparison of two preventive strategies; Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions; 2012; vol. 79 (no. 6); 929-37

Study details

Study location	USA
Study setting	single centre
Duration of follow-up	48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine sCr >141µmol/l in non-diabetics and >124µmol/l in diabetics or eGFR <50ml/min/1.73m2(MDRD) Age >18 years of age Other Patients with renal insufficiency scheduled for diagnostic or interventional angiography
Exclusion criteria	Other conditions Pulmonary oedema; Serum bicarbonate >34mmol/l; cardiogenic shock Allergy Allergy to contrast media Medications RRT; Fenoldopam, mannitol, dopamine or NAC within 48h prior to index procedure Pregnancy or breastfeeding Serum creatinine Change in sCr of >0.4mg/dl within 48h prior to index procedure Did not provide consent
Sample size	320

Loss to follow-up	0
Interventions	Contrast type Low-osmolar Contrast name iodixanol, iopamidol, ioversol Contrast dose, ml, mean (SD) 110 (IQR 80-150) ml Contrast procedure diagnostic or interventional angiography
Outcome measures	Contrast induced AKI at 48 hours, defined as an increase in sCr ≥25% or 44µmol/l

Study arms

NAC + Sodium chloride 0.9% (N = 81)

Pre-procedure: oral NAC 1200mg 2-12 h before procedure, with 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours. Post-procedure: NAC 1200mg for 6-12 hours, with 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours.

% Female	group 1+2 combined: 42.9%
Mean age (SD)	group 1+2 combined: median;
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 150 % Diabetes group 1+2 combined: 45.3% % Hypertension group 1+2 combined: 93.8% % ACEI group 1+2 combined: 61.5%

Sodium chloride 0.9% (N = 80)

Pre-procedure: 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours. Post-procedure: 0.9% sodium chloride at a dose of 1ml/kg/h for 12 hours.

% Female	group 1+2 combined:; 42.9%
Mean age (SD)	group 1+2 combined:; median 73 (IQR 63-80 years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 141 % Diabetes group 1+2 combined: 45.3% % Hypertension group 1+2 combined: 93.8% % ACEI group 1+2 combined: 61.5%

NAC + sodium bicarbonate (N = 80)

Pre-procedure: oral NAC 1200mg 2-12 h before procedure, with sodium bicarbonate at a dose of 3ml/kg/h for 1 hour. Post-procedure: NAC 1200mg for 6-12 hours, with sodium bicarbonate at a dose of 1ml/kg/h for 6 hours.

% Female	group 1+2 combined: 43.4%
Mean age (SD)	group 1+2 combined: median;
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 150 % Diabetes group 1+2 combined: 49.1% % Hypertension group 1+2 combined: 95.0% % ACEI group 1+2 combined: 55.4%

Sodium bicarbonate (N = 79)

Pre-procedure: sodium bicarbonate at a dose of 3ml/kg/h for 1 hour. Post-procedure: sodium bicarbonate at a dose of 1ml/kg/h for 6 hours.

% Female	group 1+2 combined: 43.4%
Mean age (SD)	group 1+2 combined:; median 74 (IQR 65-80) years

	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 150 % Diabetes group 1+2 combined: 49.1% % Hypertension group 1+2 combined: 95.0% % ACEI group 1+2 combined: 55.4%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Heng 2008

Bibliographic Reference	Heng AE; Cellarier E; Aublet-Cuvelier B; Decalf V; Motreff P; Marcaggi X; Deteix P; Souweine B; Is treatment with N-acetylcysteine to prevent contrast-induced nephropathy when using bicarbonate hydration out of date?; Clinical nephrology; 2008; vol. 70 (no. 6); 475-484

Study details

Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	Single hospital centre
Study dates	January 2002 and November 2004
Duration of follow-up	48 hours
Sources of funding	Delegation a la Recherche Clinique (PHRC local)
Inclusion criteria	Serum creatinine stable serum creatinine concentrations defined as a difference lower than 0.1 mg/dl (8.8 µmol/l) between a serum creatinine level measured 1– 2 months before cardiac angiography and the baseline level measured within 24 hours before cardiac angiography eGFR rate below 56 ml/min received imaging Patients scheduled for cardiac angiography either elective coronary angiography and/or percutaneous coronary intervention Chronic kidney disease
Exclusion criteria	Other conditions vert congestive heart failure Allergy Allergy to NAC Medications administration of iodinated contrast media or nephrotoxic agents or NAC in the 30 days before inclusion; Patients being treated with nephrotoxic agents such as nonsteroidal antiinflammatory drugs or aminosides at the time of the study Age <18 years old History of dialysis Pregnancy or breastfeeding

	Pregnancy Related conditions Acute renal failure Blood pressure hemodynamic instability (systolic blood pressure < 90 mmHg or diastolic < 50 mmHg)
Sample size	77
Loss to follow-up	17
Interventions	Contrast type nonionic, low-osmolarity or nonionic iso-osmolar contrast media Contrast name Iomeprol (Iomeron) or iodixanol (Visipaque) Contrast procedure Coronary angiography, ventriculography and angioplasty
Outcome measures	Adverse events major adverse cardiac events (cardiac death, nonfatal myocardial infarction (defined as > 0.3 times the upper limit of creatine kinase-MB levels), and acute congestive heart failure) Need for dialysis CIN increase in serum creatinine of ≥ 44.2 µmol/l (0.5 mg/dl) (criterion a), increase in serum creatinine ≥25% (criterion b), and decline in GFR of ≥ 5 ml/min, (criterion c) within 48 hours. Where alternative explanations for renal impairment had been excluded.

Study arms

	oral NAC + IV sodium bicarbonate (N = 28) NAC dose: 1,200 mg twice daily, given three times prior to contrast and once after: Sodium bicarbonate: 1.4% intravenously at a rate of 1 ml/kg of body weight/hour for 12 hours pre-contrast and 12 hours after

Sample size	39
Loss to follow-up	11
% Female	21

Mean age (SD)	74
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 178 (53) % Diabetes 39 % Hypertension 86 % ACEI ACEi or ARB: 32%
Interventions	Contrast dose, ml, mean (SD) 208 (70)

matching placebo + IV sodium bicarbonate (N = 32)

Matching placebo: 1,200 mg twice daily, given three times prior to contrast and once after. Sodium bicarbonate: 1.4% intravenously at a rate of 1 ml/kg/hour for 12 hours pre-contrast and 12 hours after

Sample size	32
Loss to follow-up	6
% Female	22
Mean age (SD)	72 (8)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 193 (76) % Diabetes 12 (37) % Hypertension 91 % ACEI ACEi or ARB: 47%
Interventions	Contrast dose, ml, mean (SD) 198 (76)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(unclear if allocation concealment; significant exclusions post randomisation which were unbalanced between treatment arms; trial stopped early with unclear stopping rules; possibility that reason for missing outcome data could be related to absence of CIN event)

Overall Directness

Directly applicable

Hsu 2007

Bibliographic Reference	Hsu C; Lee J; Lo P; Lin J; Chang H; Chou H; Prevention of radiocontrast-induced nephropathy with N-acetylcysteine after cardiac angiography in diabetic patients with renal dysfunction; Mid-Taiwan Journal of Medicine; 2007; vol. 12 (no. 4)

Study details

Study type	Randomised controlled trial (RCT)

Study location	Taiwan
Study setting	Single hospital setting
Study dates	July 2003 to July 2005
Duration of follow-up	5 days for CIN outcomes, and length of hospitalisation otherwise.;
Sources of funding	None reported
Inclusion criteria	Serum creatinine baseline SCC ≥ 1.6 mg/dL or estimated creatinine clearance (CCR) < 40 mL/min, Diabetes mellitus and an elevated HbA1c received imaging Cardiac angiography and received a volume of radiocontrast (iohexol) greater than 1.5 mL/kg
Exclusion criteria	Other conditions active congestive heart failure, left ventricular ejection fraction < 40% by M-mode echocardiography, acute coronary syndrome requiring immediate intervention Contrast exposure to contrast media or other nephrotoxic agents within the previous 30 days; exposure to contrast media other than iohexol Medications exposure to aminophylline, dopamine or mannitol from one week before the procedure until the end of the study Age <18 years old History of dialysis within the past 30 days Related conditions unstable renal function (including end stage renal disease), active urinary tract infection, acute renal failure Blood pressure Shock Serum creatinine serum creatinine measurements varied by more than 15% thirty days prior to angiography other heavy proteinuria (urinary protein >300 mg/dL in spot urine) or gross hematuria

Sample size	20
Loss to follow-up	none reported
% Female	50
Mean age (SD)	Range: 44 - 84
Interventions	Contrast type nonionic, low osmolar Contrast name iohexol (ominplaque) Contrast dose, ml, mean (SD) 188.6 (57.9) Contrast procedure Coronary angiography and/or angioplasty

Study arms

oral NAC + IV sodium chloride 0.45% (N = 11)

NAC dose: 600 mg/twice a day. 2 doses pre-contrast and 2 doses post contrast (total oral NAC 1200mg daily for 2 days) Sodium chloride 0.45% dose: 1ml/kg/h. 12 hours prior to contrast and 12 hours post contrast.

Sample size	11
% Female	36.4
Mean age (SD)	Range: 44 - 84;
Condition specific characteristics	% Hypertension 82.0 % ACEI 18 % NSAIDs Aspirin: 82.0% Baseline serum creatinine, mg/dl, mean (SD) 2.8 (1.0)
Interventions	Contrast dose, ml, mean (SD)

	206.5 (67.5)

matched placebo + IV sodium chloride 0.45% (N = 9)

Matched placebo dose: 600 mg/twice a day. Two doses before and after contrast. Sodium chloride 0.45%: 1 mL/kg/h. 12 hours before contrast and 12 hours after contrast

Sample size	9
% Female	66.6
Mean age (SD)	Range: 44 -;
Condition specific characteristics	% Hypertension 100 % ACEI 56 % NSAIDs Aspirin: 100 Baseline serum creatinine, mg/dl, mean (SD) 2.6 (0.8)
Interventions	Contrast dose, ml, mean (SD) 166.7 (35.8)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

High

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

High

Overall bias and Directness

Risk of bias judgement

High

(Trial terminated early; unclear if planned interim analysis or if stopping rules; unclear if allocation concealment; some differences between study arms in terms of baseline characteristics; single blind; unclear if data was available for all randomised participants; CIN only reported at 5 days post procedure but also measured 2 days post procedure.)

Overall Directness

Directly applicable

Jaffery 2012

Bibliographic Reference	Jaffery, Z.; Verma, A.; White, C. J.; Grant, A. G.; Collins, T. J.; Grise, M. A.; Jenkins, J. S.; McMullan, P. W.; Patel, R. A.; Reilly, J. P.; et al.; A randomized trial of intravenous n-acetylcysteine to prevent contrast induced nephropathy in acute coronary syndromes; Catheterization and cardiovascular interventions; 2012; vol. 79 (no. 6); 921-926

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	single centre
Study dates	January 2007- October 2010
Duration of follow-up	72 hours
Sources of funding	None reported
Inclusion criteria	Age at least 18 years of age

	Other Patients with acute coronary syndrome undergoing coronary angiography or percutaneous coronary intervention.
Exclusion criteria	Contrast Known hypersensitivity to NAC or a history of life threatening contrast reaction History of dialysis ESRD requiring RRT
Sample size	398
Loss to follow-up	0
% Female	36.7%
Mean age (SD)	65.4 (SD 12.8) years
Interventions	Contrast type Iso-osmolar, non-ionic Contrast name iodixanol Contrast dose, ml, mean (SD) 165.6 (SD 89.3) ml Contrast procedure undergoing coronary angiography or percutaneous coronary intervention.
Outcome measures	Contrast induced AKI at 72 hours, increase in sCr ≥25% from baseline Mortality at 30 days and in-hospital mortality Length of hospital stay in days Renal failure need for RRT

Study arms

	IV NAC + sodium chloride 0.9% (N = 206) IV NAC: 1200 mg bolus followed by 200mg /h for 24hrs (iv solution consisted of 6g NAC in 500ml of 5% dextrose solution in water)). IV sodium chloride 0.9%, “the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs”. *Unclear timing

% Female	33%
Mean age (SD)	65.6 (SD 12.9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 96 (SD 3.5) umol/L % Diabetes 35.4% % Hypertension 73.8%

Sodium chloride 0.9% (N = 192)

IV sodium chloride 0.9%, “the total volume of fluid administered was equal to 1 ml/kg/h for 24hrs”. *Unclear timing

% Female	40.6%
Mean age (SD)	65.1;(SD 12.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 95 (SD 3.5) umol/L % Diabetes 21.4% % Hypertension 71.9%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(only concerns: unclear if allocation concealment and not enough information regarding randomisation process)

Overall Directness

Directly applicable

Kama 2014

Bibliographic Reference	Kama, Ahmet; Yilmaz, Serkan; Yaka, Elif; Dervisoglu, Erkan; Dogan, Nurettin Ozgur; Erimsah, Emre; Pekdemir, Murat; Comparison of short-term infusion regimens of N-acetylcysteine plus intravenous fluids, sodium bicarbonate plus intravenous fluids, and intravenous fluids alone for prevention of contrast-induced nephropathy in the emergency department; Academic emergency medicine : official journal of the Society for Academic Emergency Medicine; 2014; vol. 21 (no. 6); 615-22

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	The study site was an academic tertiary hospital in the western Anatolian region of Turkey.
Study dates	January 1, 2011 to December 21, 2011
Duration of follow-up	measures taken up to 72 hours after treatment.
Sources of funding	No commercial support has been accepted related to the development or publication of this activity.

Inclusion criteria	Age 18 years or older received imaging received contrast-enhanced CT as part of emergency care Moderate to high CIN risk according to Mehran score for CIN Other whose presentations and follow-up creatinine levels were obtained
Exclusion criteria	Other conditions hemodynamically unstable requiring excessive fluid resuscitation or surgery Allergy history of contrast related allergy Medications receiving renal replacement therapy Did not provide consent
Sample size	107
Loss to follow-up	471 patients met inclusion criteria, only 107 completed second blood draws to determine outcome.
Interventions	Contrast type Non-ionic, low-osmolality Contrast name Iohexal Contrast dose, ml, mean (SD) <100ml Contrast procedure CT scan
Outcome measures	Contrast induced AKI defined as a 25% increase or a greater than 0.5 mg/dL (44 lmol/L) increase in the serum creatinine level, 48 to72 hours after the administration of contrast agent compared with the baseline creatinine measurement. Renal failure renal failure necessitating renal replacement therapy

Study arms

	IV NAC + IV sodium chloride 0.9% (N = 36)

Pre, during and after contrast: 150 mg/kg NAC in 1,000 mL of 0.9% NaCl at a rate of 350 mL/hour.

% Female	30.6%
Mean age (SD)	69 years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 143.2 umol/L % Diabetes 42% Baseline eGFR, ml/min per 1.73m2, mean (SD) 44 (33.5-54.4)

IV sodium chloride 0.9% + IV sodium dicarbonate (N = 36)

Pre, during and after contrast: 150 mEq in 1,000 mL of 0.9% NaCl at a rate of 350 mL/hour.

% Female	34.7%
Mean age (SD)	76 years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 131.72 umol/L % Diabetes 31% Baseline eGFR, ml/min per 1.73m2, mean (SD) 43.5 (33.5 - 53.5)

IV sodium chloride 0.9% (N = 35)

Pre, during and after contrast: 1,000 mL 0.9% NaCl infusion of 350 mL/hour.

% Female	32.7%
Mean age (SD)	67 years

	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 129.9 umol/L % Diabetes 25.8% Baseline eGFR, ml/min per 1.73m2, mean (SD) 49.7 (39.2-60.3)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(Per-protocol analysis with >5% exclusions in either arm; unclear if allocation concealment; More information about the reasons for exclusion desirable.)

Overall Directness

Directly applicable

Kay 2003

Bibliographic Reference	Kay J; Chow WH; Chan TM; Lo SK; Kwok OH; Yip A; Fan K; Lee CH; Lam WF; Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial.; JAMA; 2003; vol. 289 (no. 5)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Hong Kong
Study setting	University hospital
Study dates	May 2000-December 2001
Duration of follow-up	up to 7 days
Sources of funding	Zambon Group S.p.A, Milan, Italy (manufacturers of NAC) prepared NAC and placebo
Inclusion criteria	Other stable chronic renal impairment and stable sCr (sCr >106µmol/l, CrCl <60ml/min) undergoing elective coronary angiography with or without intervention
Exclusion criteria	Other conditions Overt congestive heart failure, severe valvular disease or LVEF <35%; COPD or asthma exacerbation Allergy to NAC; or acute renal failure Allergy allergy to NAC Contrast Received iodinated contrast media or nephrotoxic agents within 30 days Medications “Change in use” of diuretic or antihypertensive agents History of dialysis need for RRT
Sample size	200
Loss to follow-up	8
Interventions	Contrast type Non-ionic low osmolar Contrast name iopamidol

	Contrast dose, ml, mean (SD) at discretion of cardiologist; mean 139 (SD 53) ml Contrast procedure elective coronary angiography
Outcome measures	Contrast induced AKI at 48 hours, increase in sCr ≥25% 48h after contrast administration Mortality in hospital Adverse events due to study drug – nausea causing discontinuation of study drug Length of hospital stay Renal failure need for RRT

Study arms

	oral NAC + sodium chloride 0.9% (N = 102) Pre-procedure: 600mg NAC twice daily, starting the day before and given for 3 doses. IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 12 hours. Post-procedure: 600mg NAC given for one dose. IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 6 hours.

% Female	40.2%
Mean age (SD)	median 69 (IQR 50-81)
Condition specific characteristics	Baseline serum creatinine, µmol/l, (median [IQR]) 109.6 [68.1-264.3] umol/L % CKD 100% % Diabetes 39.2% % Hypertension 38.2% % ACEI 39.2%
Interventions	Contrast type Non-ionic low osmolar

	Contrast name iopamidol Contrast dose, ml, mean (SD) at discretion of cardiologist Contrast procedure elective coronary angiography

Sodium chloride 0.9% (N = 98)

Pre-procedure: IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 12 hours. Post-procedure: IV sodium chloride 0.9% at a dose of 1ml/kg/hour for 6 hours.

% Female	36.7%
Mean age (SD)	median 69 (48-82) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, median [IQR] 111.4 [66.3-321.8] umol/L % CKD 100% % Diabetes 35.7% % Hypertension 42.9% % ACEI 39.8%
Interventions	Contrast type Non-ionic low osmolar Contrast name iopamidol Contrast dose, ml, mean (SD) at discretion of cardiologist Contrast procedure elective coronary angiography

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Khalili 2006

Bibliographic Reference	Khalili H; Dashti-Khavidaki S; Tabifar H; Ahmadinejad N; Ahmadi F; N-acetylcysteine in the prevention of contrast agent-induced nephrotoxicity in patients undergoing computed tomography studies; Therapy; 2006; vol. 3 (no. 6)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	unclear
Duration of follow-up	72 hours

Sources of funding	supported by Tehran University of Medical Sciences and a Health Services grant.
Inclusion criteria	Serum creatinine stable SCr during the 3 days prior to procedure Chronic kidney disease known history of chronic kidney disease (serum creatinine [SCr] concentration above 106.1 umol/L or creatinine clearance [CrCl] of less than 60 ml/min)
Exclusion criteria	Other conditions acute renal failure Medications treated with theophylline, calcium channel blockers, dopamine receptor agonists or diuretics
Sample size	70
Loss to follow-up	0
Interventions	Contrast type nonionic, low-osmolar Contrast name Iohexel Contrast dose, ml, mean (SD) 140 ml Contrast procedure elective abdominal or CT scanning
Outcome measures	Contrast induced AKI at 48 and 72 hours, defined as defined as an increase of at least 25% of baseline in the SCr concentration

Study arms

	Oral NAC + IV sodium chloride 0.9% (N = 35) Pre-procedure: NAC 1200mg once daily, on the day before imaging and at the day of contrast. 1000ml IV sodium chloride 0.9% given at a dose of 1ml/kg/hour prior to procedure.

% Female	42.9%
Mean age (SD)	59.76 (1.99) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 126.41 (32.71) umol/L % Diabetes 40%

IV sodium chloride 0.9% (N = 35)

Pre-procedure: 1000ml IV sodium chloride 0.9% given at a dose of 1ml/kg/hour prior to procedure.

% Female	37.1%
Mean age (SD)	55.89 (12.92)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 115.8 (13.26) umol/L % Diabetes 31.4%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if allocation concealment; unclear how randomisation was performed; unclear statistical methods used to analyse dichotomous outcomes; protocol provides minimal information)

Overall Directness

Directly applicable

Kitzler 2012

Bibliographic Reference	Kitzler TM; Jaberi A; Sendlhofer G; Rehak P; Binder C; Petnehazy E; Stacher R; Kotanko P; Efficacy of vitamin E and N-acetylcysteine in the prevention of contrast induced kidney injury in patients with chronic kidney disease: a double blind, randomized controlled trial.; Wiener klinische Wochenschrift; 2012; vol. 124 (no. 910); 312-319

Study details

Study type	Randomised controlled trial (RCT)
Study location	Austria
Study setting	Single hospital centre
Study dates	August 2002 to July 2003
Duration of follow-up	48 hours
Sources of funding	Fresenius Kabi Austria (Industry)
Inclusion criteria	Serum creatinine > 1.25 mg/dL for males and 1.09 mg/dL for females Age ≥18 years old
Exclusion criteria	Allergy known or suspected allergy to the investigational drugs; current use of a theophylline, dopamine, furosemide, or mannitol Medications administration of vitamin E, NAC, or other antioxidant therapy within 4 weeks prior;

	History of dialysis Related conditions Acute kidney injury Serum creatinine a serum creatinine increase in the enrollment period of more than 0.2 mg/dL other participation in an investigational clinical trial within 1 month prior to the start of the study
Sample size	20
Loss to follow-up	1
Interventions	Contrast type nonionic low-osmolar Contrast name iopromide (Ultravist) Contrast dose, ml, mean (SD) not reported Contrast procedure elective diagnostic radiocontrast CT
Outcome measures	CIN an increase in serum creatinine of more than 25 % over the baseline value in the 48 h following CT scan

Study arms

	oral NAC + IV sodium chloride 0.45% + placebo emulsion (N = 10) NAC: granules 1200 mg, 12 and 6 hours before and 12 and 6 hours after contrast (total oral NAC 2400mg daily for 2 days) sodium chloride 0.45%: 1 ml/kg/h 12 hours before and 12 hours after contrast placebo emulsion: 540 mg for 30 min (placebo for vitamin E). Received 12 and 6 hours before contrast and 6 and 12 hours after contrast.

Sample size	10
Loss to follow-up	0
% Female	80

Mean age (SD)	76.6 (9.5)
Condition specific characteristics	% CKD 100 % Diabetes 30 % Hypertension 80 % ACEI ACEi or ARB: 40% Baseline serum creatinine, mg/dl, mean (SD) 1.37 (0.51)
Interventions	Contrast dose, ml, mean (SD) not reported

placebo + IV sodium chloride 0.45% (N = 10)

Placebo granules: granules 1200 mg, 12 and 6 hours before and 12 and 6 hours after contrast Sodium chloride 0.45%: 1 ml/kg/h 12 hours before and 12 hours after contrast Placebo emulsion: 540 mg for 30 min (placebo for vitamin E). Received 12 and 6 hours before contrast and 6 and 12 hours after contrast.

Sample size	10
% Female	50
Mean age (SD)	74 (8.5)
Condition specific characteristics	% Diabetes 30 % Hypertension 70 % ACEI ACEi or ARB: 70% Baseline serum creatinine, mg/dl, mean (SD) 1.33 (0.12)
Interventions	Contrast dose, ml, mean (SD) not reported

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(An otherwise well-conducted study, however early termination due to no trend towards any study arm being superior.)

Overall Directness

Directly applicable

Koc 2012

Bibliographic Reference	Koc, Fatih; Ozdemir, Kurtulus; Kaya, Mehmet Gungor; Dogdu, Orhan; Vatankulu, Mehmet Akif; Ayhan, Selim; Erkorkmaz, Unal; Sonmez, Osman; Aygul, Meryem Ulku; Kalay, Nihat; Kayrak, Mehmet; Karabag, Turgut; Alihanoglu, Yusuf; Gunebakmaz, Ozgur; Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS--a multicenter prospective controlled trial; International journal of cardiology; 2012; vol. 155 (no. 3); 418-23

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study dates	Unclear
Duration of follow-up	Unclear
Sources of funding	none reported
Inclusion criteria	Serum creatinine creatinine clearance 60ml/min or less and/or baseline serum creatining level 1.1 mg/dL or more. Age at least 18 years of age
Exclusion criteria	Other conditions decompensated heart failure, pulmonary edema, emergency catheterization, acute renal failure or end-stage renal failure. Contrast contrast-agent hypersensitivity Pregnancy or breastfeeding
Sample size	220
Loss to follow-up	none reported
Interventions	Contrast type low-osmolar, nonionic iohexol Contrast name Omnipaque Contrast dose, ml, mean (SD) 138±47 mL Contrast procedure Coronary angiography and PCI
Outcome measures	CIN alteration in SCr levels 48 hours after the administration of the contrast media. The secondary end point was the development of CIN after the procedure. CIN was described as a baseline SCr≥25% and/or an absolute increase in SCr of ≥0.5 mg/dL 48 hours after the procedure

Study arms

IV NAC + IV sodium chloride 0.9% (N = 80)

IV bolus of 600 mg of NAC twice daily before and on the day of the coronary procedure (total=2.4 g) plus IV 0.9% saline 1 mL/ kg/h before, on and after the day of the coronary procedure.

% Female	24%
Mean age (SD)	62 (SD10) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 114.9 (IQR 106.1 - 132.6) umol/L % CKD 38% % Diabetes 38% % Hypertension 54% % ACEI 75% ACEI or ARB

IV sodium chloride 0.9% (N = 80)

IV 0.9% saline 1 mL/kg/h before, on and after the day of coronary procedure.

% Female	21%
Mean age (SD)	65 (SD11) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 114.9 (IQR 106.1 - 123.8) umol/L % Diabetes 26% % Hypertension 48% hypertension % ACEI 37% ACI or ARB

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear how randomisation was performed; unclear if allocation concealment; unclear if definitely no exclusions or missing data post randomisation; control group received less IV hydration)

Overall Directness

Directly applicable

Kooiman 2014a

Bibliographic Reference	Kooiman, Judith; Sijpkens, Yvo W. J.; de Vries, Jean-Paul P. M.; Brulez, Harald F. H.; Hamming, Jaap F.; van der Molen, Aart J.; Aarts, Nico J. M.; Cannegieter, Suzanne C.; Putter, Hein; Swarts, Renate; van den Hout, Wilbert B.; Rabelink, Ton J.; Huisman, Menno V.; A randomized comparison of 1-h sodium bicarbonate hydration versus standard peri-procedural saline hydration in patients with chronic kidney disease undergoing intravenous contrast-enhanced computerized tomography; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2014; vol. 29 (no. 5); 1029-36

Study details

Study location	The Netherlands
Study setting	one academic and three non-academic Dutch hospitals
Study dates	January 2010 - June 2012
Duration of follow-up	up to 2 months
Sources of funding	The study was funded by the Bronovo Hospital Research Foundation, a charity foundation. The sponsor did not have any influence on the design of the trial, data collection, analyses, interpretation or the writing of this manuscript.
Inclusion criteria	Age at least 18 years of age Chronic kidney disease eGFR < 60 mL/min/1.73 m2 estimated by the Modification of Diet in Renal Disease formula and were eligible for the fluid challenge of saline hydration.
Exclusion criteria	Other conditions haemodynamic instability (systolic blood pressure <100 mmHg) Allergy documented allergy for iodinated contrast media Contrast previous contrast administration within the last 7 days Pregnancy or breastfeeding Procedures previous participation in the trial
Sample size	548 included in ITT sample
Loss to follow-up	35 participants had missing primary endpoint data *22 participants withdrew informed consent (not included in ITT sample)
Interventions	Contrast type low-osmolar contrast media in all hospital Contrast name Iomeron, Xenetix, Visipaque Contrast procedure CE-CT
Outcome measures	Contrast induced AKI Adverse events acute heart failure due to volume expansion

	Readmission for AKI rehospitalization or outpatient visit Renal failure recovery of renal function in CI-AKI patients [recovery defined as an increase in serum creatinine <25% or <44 µmol/L (0.5 mg/dL) measured at 2 months post-CE-CT compared with baseline] Serum creatinine clearance relative increase in serum creatinine measured between 48 and 96 h post-CE-CT compared with baseline. Need for dialysis

Study arms

	Sodium bicarbonate (N = 281) 250 mL intravenous 1.4% sodium bicarbonate 1 h prior to CE-CT without hydration post-CE-CT

% Female	40.1%
Mean age (SD)	71.6 (SD 9.8) years
Condition specific characteristics	% Diabetes 26.6% % ACEI 40.1% % NSAIDs 3.0% Baseline eGFR, ml/min per 1.73m2, mean (SD) 49.9 (SD 13.4)
Interventions	Contrast type low-osmolar contrast media in all hospital Contrast name Iomeron, Xenetix, Visipaque Contrast dose, ml, mean (SD) 105.7 (SD 21.0) Contrast procedure CE-CT

	IV Sodium chloride 0.9% (N = 289)

	2000 mL of 0.9% saline, 1000 mL prior to and 1000 mL post-CE-CT	
	% Female	39.1%
	Mean age (SD)	72.5 *SD 9.5) years
	Condition specific characteristics	% Diabetes 27.0% % ACEI 38.4% % NSAIDs 6.8% Baseline eGFR, ml/min per 1.73m2, mean (SD) 50.9 (SD 13.9)
	Interventions	Contrast type low-osmolar contrast media in all hospital Contrast name Iomeron, Xenetix, Visipaque Contrast dose, ml, mean (SD) 104.7 (21.6) Contrast procedure CE-CT

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(However, unclear if allocation concealment)

Overall Directness

Directly applicable

Kooiman 2014b

Bibliographic Reference	Kooiman, J.; Sijpkens, Y. W. J.; van Buren, M.; Groeneveld, J. H. M.; Ramai, S. R. S.; van der Molen, A. J.; Aarts, N. J. M.; van Rooden, C. J.; Cannegieter, S. C.; Putter, H.; Rabelink, T. J.; Huisman, M. V.; Randomised trial of no hydration vs. sodium bicarbonate hydration in patients with chronic kidney disease undergoing acute computed tomography-pulmonary angiography; Journal of thrombosis and haemostasis : JTH; 2014; vol. 12 (no. 10); 1658-66

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Three non-academic and one academic teaching hospitals.
Study dates	November 2009 to June 2013
Duration of follow-up	up to 2 months
Sources of funding	The study was funded by the Bronovo Hospital Research Foundation, a Charity Foundation. The sponsor had no influence on the design of the trial, data collection, analyses, interpretation, or writing of the manuscript.
Inclusion criteria	Age at least 18 years old Other

	high clinical suspicion of acute PE requiring CTPA were eligible for inclusion (IE Wells score >4 or Abnormal D-dimer) Chronic kidney disease eGFR < 60 mL min-1/1.73m2
Exclusion criteria	Other conditions hemodynamic instability Allergy for iodinated contrast media Contrast previous contrast administration in last 7 days Pregnancy or breastfeeding
Sample size	139
Loss to follow-up	1 person
Interventions	Contrast type type of contrast media used for CTPA was according to hospital guidelines. Three hospitals used low-osmolar contrast media (iopromide [Ultravist, Bayer Healthcare Pharmaceuticals, Leverkusen, Germany], or iobitridol [Xenetix, Guerbet, Aulnay-sous-Bois, France]), whereas the fourth center used an iso-osmolar contrast agent in all patients [iodixanol (Visipaque, GE Healthcare, Chalfort St. Giles, UK)]. Contrast name ultravist, Xenetix or visipaque Contrast procedure CTPA
Outcome measures	Contrast induced AKI incidence of CI-AKI Renal failure recovery of renal function in CI-AKI patients (increase in serum creatinine <25% or <44 umol L-1 measured at 2 months after CTPA compared with baseline Serum creatinine clearance serum creatinine increase measured between 48 and 96 h after CTPA compared with baseline. Need for dialysis

Study arms

	no hydration (N = 67)

No hydration given

% Female	47.8%
Mean age (SD)	70.0 (12.4)
Condition specific characteristics	% Diabetes 14.9% % ACEI 34.4% % NSAIDs 7.8% Baseline eGFR, ml/min per 1.73m2, mean (SD) 50.2 (15.5)
Interventions	Contrast type type of contrast media used for CTPA was according to hospital guidelines. Three hospitals used low-osmolar contrast media (iopromide [Ultravist, Bayer Healthcare Pharmaceuticals, Leverkusen, Germany], or iobitridol [Xenetix, Guerbet, Aulnay-sous-Bois, France]), whereas the fourth center used an iso-osmolar contrast agent in all patients [iodixanol (Visipaque, GE Healthcare, Chalfort St. Giles, UK)]. Contrast name ultravist, Xenetix or visipaque Contrast dose, ml, mean (SD) Contrast volume 74.5 (10.3) ml; Iodine dose 24.9 (3.8) g Contrast procedure CTPA

IV Sodium bicarbonate (N = 72)

Pre CTPA: 250 mL intravenous 1.4% sodium bicarbonate 1h Post-CTPA: Without hydration.

% Female	52.1%
Mean age (SD)	71.1 (13.3) years
Condition specific characteristics	% Diabetes % ACEI

		25.0% % NSAIDs 4.4%
	Interventions	Contrast type type of contrast media used for CTPA was according to hospital guidelines. Three hospitals used low-osmolar contrast media (iopromide [Ultravist, Bayer Healthcare Pharmaceuticals, Leverkusen, Germany], or iobitridol [Xenetix, Guerbet, Aulnay-sous-Bois, France]), whereas the fourth center used an iso-osmolar contrast agent in all patients [iodixanol (Visipaque, GE Healthcare, Chalfort St. Giles, UK)]. Contrast name ultravist, Xenetix or visipaque Contrast dose, ml, mean (SD) Contrast volume: 73.5 (SD 8.1) ml; iodine dose: 24.7 (SD 3.1) g Contrast procedure CTPA

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(although unclear if allocation concealment)

Overall Directness

Directly applicable

Kooiman 2018

Bibliographic Reference	Kooiman, Judith; de Vries, Jean-Paul P. M.; Van der Heyden, Jan; Sijpkens, Yvo W. J.; van Dijkman, Paul R. M.; Wever, Jan J.; van Overhagen, Hans; Vahl, Antonie C.; Aarts, Nico; Verberk-Jonkers, Iris J. A. M.; Brulez, Harald F. H.; Hamming, Jaap F.; van der Molen, Aart J.; Cannegieter, Suzanne C.; Putter, Hein; van den Hout, Wilbert B.; Kilicsoy, Inci; Rabelink, Ton J.; Huisman, Menno V.; Randomized trial of one-hour sodium bicarbonate vs standard periprocedural saline hydration in chronic kidney disease patients undergoing cardiovascular contrast procedures; PloS one; 2018; vol. 13 (no. 2); e0189372

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	one academic hospital, and seven non-academic teaching hospitals
Study dates	2011-2014
Duration of follow-up	up to 2 months; following procedure.
Sources of funding	The study was funded by the Bronovo Hospital Research Foundation, a charity foundation. The sponsor did not have any influence on the design of the trial, data collection, analyses, interpretation or the writing of this manuscript.
Inclusion criteria	Age at least 18 years old eGFR < 45 ml/min, or an eGFR 45±60 ml/min in combination with diabetes mellitus or at least two other risk factors for the development of CI-AKI (i.e. peripheral arterial disease, congestive heart failure, age > 75 years, anemia, use of diuretics or non-steroidal anti-inflammatory drugs)
Exclusion criteria	Other conditions Currently have acute kidney injury Allergy

	for iodinated contrast media Contrast received iodinated contrast media in the preceding seven days History of dialysis on dialysis treatment Pregnancy or breastfeeding
Sample size	333
Loss to follow-up	10 with missing endpoint data
Interventions	Contrast type varied between the 8 practices, used in accordance with clinical practice and using either: Iobitridol, Iodixanol or Iopromide. Contrast name Xenetix, Visipaque or Ultra-vist Contrast dose, ml, mean (SD) Concentrations of 270, 300, 320, and 370 mg I/ml Contrast procedure varied between practices, including: angiography, digital substration angiography, percutaneous coronary intervention, endovascular aneurism repair, coronary angiography or percutaneous coronary intervention
Outcome measures	Contrast induced AKI incidence of CI-AKI (at 48±96 hours following contrast exposure) Readmission for AKI re-hospitalization and outpatient visits within 2 months follow-up Renal failure recovery of renal function (i.e. no longer fulfilling the criteria of CI-AKI compared with baseline) Serum creatinine clearance relative increase in serum creatinine (%) measured once in the 48±96 hours following contrast exposure compared with baseline Need for dialysis

Study arms

	IV sodium bicarbonate (N = 168) 1-hour pre-procedural intravenous hydration using 250 ml 1.4% sodium bicarbonate

% Female	37.5%
Mean age (SD)	73.0 (SD 9.2) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) not reported % Diabetes 35.7% % ACEI 45.2% Baseline eGFR, ml/min per 1.73m2, mean (SD) 50.0 (SD 14.8)

IV sodium chloride 0.9% (N = 165)

peri-procedural intravenous hydration with 0.9% saline, 1000 ml in 4±12 hours prior to and 1000 ml in 4±12 hours following contrast administration (total volume 2000 ml).

% Female	33.3%
Mean age (SD)	72.5 (SD 8.8) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) not reported % Diabetes 38.8% % ACEI 47.3% Baseline eGFR, ml/min per 1.73m2, mean (SD) 51.1 (SD 16.7)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Kotlyar 2005

Bibliographic Reference	Kotlyar E; Keogh AM; Thavapalachandran S; Allada CS; Sharp J; Dias L; Muller D; Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures--a randomised controlled trial.; Heart, lung & circulation; 2005; vol. 14 (no. 4); 245-251

Study details

Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Single hospital centre
Study dates	February 2002 to October 2002
Duration of follow-up	30 days
Sources of funding	Mayne Pharma grant (industry)

Inclusion criteria	Serum creatinine serum creatinine ≥0.13 mmol/l; received imaging undergoing elective coronary, carotid or peripheral angiography and/or PTCA and stenting
Exclusion criteria	Other conditions uncontrolled asthma Allergy allergy to the study medication History of dialysis currently on dialysis Pregnancy or breastfeeding Serum creatinine unstable renal function (creatinine rising by ≥0.04 mmol/(l day))
Sample size	65
Loss to follow-up	5
Interventions	Contrast type nonionic, low-osmolarity Contrast name Iopromide (Ultravist) Contrast procedure coronary or peripheral angiography and/or stenting
Outcome measures	Adverse events clinical adverse events including allergic reaction to the study medication, need for haemodialysis and congestive cardiac failure CIN an increase in the serum creatinine concentration of at least 0.044 mmol/l

Study arms

	IV NAC 300mg + IV sodium chloride 0.9% (N = 20) NAC dose: 300mg prepared in 100 ml of 5% dextrose and administered over 20 min. 2 hours before contrast and 2 - 4 hours post contrast. IV sodium chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast. Sample size: 20

Loss to follow-up	none reported
% Female	25.0
Mean age (SD)	66 (14)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 160 (30) % Diabetes 35 % Hypertension 65 % ACEI ACEi or ARB: 40%
Interventions	Contrast dose, ml, mean (SD) 87 (34)

IV NAC 600mg + IV sodium chloride 0.9% (N = 21)

NAC dose: 600mg prepared in 100 ml of 5% dextrose and administered over 20 min. 2 hours before contrast and 2 - 4 hours post contrast. IV sodium chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast.

Sample size	21
Loss to follow-up	none reported
% Female	14.3
Mean age (SD)	67 (12)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 160 (30) % Diabetes 29 % Hypertension 71 % ACEI ACEi or ARB: 33%

Interventions	Contrast dose, ml, mean (SD) 89 (32)

IV sodium chloride 0.9% (N = 19)

IV sodium chloride dose: 200 ml/h. from 2 hours before contrast until 5 hours post contrast.

Sample size	19
Loss to follow-up	none reported
% Female	10.5
Mean age (SD)	69 (9)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 150 (20) % Diabetes 16 % Hypertension 68 % ACEI ACEi or ARB: 42%
Interventions	Contrast dose, ml, mean (SD) 86 (41)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Lee 2011

Bibliographic Reference	Lee, Seung-Whan; Kim, Won-Jang; Kim, Young-Hak; Park, Seong-Wook; Park, Duk-Woo; Yun, Sung-Cheol; Lee, Jong-Young; Kang, Soo-Jin; Lee, Cheol Whan; Lee, Jae-Hwan; Choi, Si Wan; Seong, In-Whan; Suh, Jon; Cho, Yoon Haeng; Lee, Nae-Hee; Cheong, Sang-Sig; Yoo, Sang-Yong; Lee, Bong-Ki; Lee, Sang-Gon; Hyon, Min-Su; Shin, Won-Yong; Lee, Se-Whan; Jang, Jae-Sik; Park, Seung-Jung; Preventive Strategies of Renal Insufficiency in Patients With Diabetes Undergoing Intervention or Arteriography (the PREVENT Trial); The American Journal of Cardiology; 2011; vol. 107 (no. 10); 1447-1452

Study details

Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	9 centres
Study dates	February 2008 - August 2009
Duration of follow-up	6 months
Sources of funding	Supported by the cardiovascular research foundation, Seoul, Korea. And a grant from the ministry for health welfare and family affairs, Seoul, Republic of Korea, as part of the Korea Health 21 R&D Project.
Inclusion criteria	Serum creatinine sCr ≥97.24 µmol/l

	Age at least 18 years of age Diabetes mellitus was defined as use of hypglycemic agents or insulin. Fasting plasma glucose >126mg/dl, or random plasma glucose ≥ 200mg/dl eGFR Estimated GFR <60 ml/min/1.73m² Other scheduled for elective coronary or endovascular angioplasty/ intervention
Exclusion criteria	Other conditions end stage renal disease on hemodialysis; multiple myeloma; pulmonary oedema; acute ST-segment elevation MI while undergoing primary PCI Contrast use of contrast media in the past 2 days Medications theophylline, dopamine, mannitol, fenoldopam and NAC Blood pressure uncontrolled hypertension (systolic >160mmHg or diastolic >100mmHg) Procedures emergency coronary angioplasty/ angiography Serum creatinine sCr ≥707.2 µmol/l eGFR Estimated GFR <15ml/min/1.73m² at rest Unable to comply with follow-up
Sample size	382
Loss to follow-up	7
Interventions	Contrast type iso-osmolar, non-ionic Contrast name iodixanol Contrast dose, ml, mean (SD) 320 mg iodine/mL Contrast procedure angioplasty
Outcome measures	Contrast induced AKI

	at 48 hours, defined as an absolute increase in the sCr concentration ≥44.2µmol/l* or ≥25% from the baseline value at 48 hrs after contrast exposure Mortality cumulative rates at 6 months Renal failure need for RRT

Study arms

	NAC + sodium bicarbonate (N = 193) Pre-procedure: NAC 1200mg orally twice daily on the day before and the day of procedure. Sodium bicarbonate given at a dose of 154 mEq/L sodium bicarbonate in dextrose and water at 3ml/kg/hour for 1 hour before contrast. Post-procedure: Sodium bicarbonate given at a dose of 154 mEq/L sodium bicarbonate in dextrose and water at 1ml/kg/hour for 1 hour during contrast and 6 hours after.

% Female	43%
Mean age (SD)	median 68.5 (IQR
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) (medians Q1 to Q3): 132.6 (114.92 -167.96) % CKD 100% % Diabetes 100% % Hypertension 77.2% % ACEI 16.6%
Interventions	Contrast type iso-osmolar, non-ionic Contrast name iodixanol Contrast dose, ml, mean (SD) median 120 (IQR 79-223); 320 mg iodine/mL Contrast procedure angioplasty

	NAC + sodium chloride (N = 189)

	Pre-procedure: NAC 1200mg orally twice daily on the day before and the day of procedure. Sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours before contrast. Post-procedure: Sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours after contrast.

% Female	28.6%
Mean age (SD)	median 67.5 (IQR 62-72) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) (medians Q1 to Q3): 132.6 (114.92 -150.28) % CKD 100% % Diabetes 100% % Hypertension 79.9% % ACEI 22.8%
Interventions	Contrast type iso-osmolar, non-ionic Contrast name iodixanol Contrast dose, ml, mean (SD) median 113 (IQR 80-220); 320 mg iodine/mL Contrast procedure angioplasty

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

MacNeill 2003

Bibliographic Reference	MacNeill, Briain D.; Harding, Scott A.; Bazari, Hasan; Patton, Kristen K.; Colon-Hernadez, Pedro; deJoseph, Denise; Jang, Ik-Kyung; Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography; Catheterization and Cardiovascular Interventions; 2003; vol. 60 (no. 4); 458-461

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Single centre
Study dates	Not reported
Duration of follow-up	3 days
Sources of funding	None reported
Inclusion criteria	Serum creatinine serum creatinine (Cr) ≥ 1.5 mg/dl on the morning of the planned procedure received imaging undergoing elective cardiac catheterization

Exclusion criteria	Allergy known sensitivity to acetylcysteine Contrast exposure to contrast within the preceding 5 days Age <21 years History of dialysis dialysis-dependent chronic renal failure Pregnancy or breastfeeding Pregnancy Related conditions acute renal failure Procedures emergent procedures,
Sample size	57
Loss to follow-up	14
% Female	14.0
Mean age (SD)	72.5 (9.5)
Interventions	Contrast type nonionic, low-osmolar Contrast name iopromide or ioxilan Contrast procedure elective cardiac angiography
Outcome measures	CIN a rise in serum creatinine of > 25% from baseline to 72 hours

Study arms

	oral NAC + IV sodium chloride 0.45% (N = 21) NAC dose: 2 doses of 600mg. 1 dose at randomization, 1 dose 4 h later pre-contrast. 3 doses at 12-h intervals post-contrast (total oral NAC 1200mg daily for 2 days and 600mg the 3rd day). sodium chloride 0.45% dose: not specified. 1 ml/kg/hr for 12 hr

for in-patients and 2 ml/kg/hr for 4 hr for day-case patients pre-contrast. 75 ml/hr for 12 h post-contrast.

Sample size	21 (after loss to follow up)
% Female	23.8
Mean age (SD)	72.5 (9.5)
Condition specific characteristics	% Diabetes 57.1 Baseline serum creatinine, mg/dl, mean (SD) 1.89 (0.38)
Interventions	Contrast dose, ml, mean (SD) 103 (52.0)

placebo + IV sodium chloride 0.45% (N = 22)

Placebo: 1 dose at randomization, 1 dose 4 h later pre-contrast. 3 doses at 12-h intervals post-contrast. sodium chloride 0.45% dose: not specified. 1 ml/kg/hr for 12 hr for in-patients and 2 ml/kg/hr for 4 hr for day-case patients pre-contrast. 75 ml/hr for 12 h post-contrast.

Sample size	22 (after loss to follow up)
% Female	4.5
Mean age (SD)	72.9 (10.3)
Condition specific characteristics	% Diabetes 36.4 Baseline serum creatinine, mg/dl, mean (SD) 1.88 (0.41)
Interventions	Contrast dose, ml, mean (SD) 116 (63.3)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process **Risk of bias judgement for the randomisation process**

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Maioli 2008

Bibliographic Reference	Maioli, Mauro; Toso, Anna; Leoncini, Mario; Gallopin, Michela; Tedeschi, Delio; Micheletti, Carlo; Bellandi, Francesco; Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention; Journal of the American College of Cardiology; 2008; vol. 52 (no. 8); 599

Study details

Study location	Italy
Study setting	secondary care
Study dates	January 2005 to March 2006
Duration of follow-up	10 days

Sources of funding	none reported
Inclusion criteria	Serum creatinine pre-angiographic estimated Cr clearance <60 ml/min Chronic kidney disease chronic kidney dysfunction who underwent planned coronary angiographic procedures
Sample size	502
Loss to follow-up	9
Interventions	Contrast type iso-osmolar, non-ionic Contrast name Iodixanol Contrast procedure coronary angiography
Outcome measures	Contrast induced AKI at 48 hours, CI-AKI was defined as ≥25% relative increase in baseline serum creatinine Mortality at 10 days Renal failure need for RRT

Study arms

	NAC + sodium bicarbonate (N = 250) Pre-procedure: NAC given at a dose of 1200mg twice daily, on the day before and day of procedure, IV sodium bicarbonate given at a dose of 154 mEq/l in dextrose and water, 3ml/kg for 1 hour before procedure. Post-procedure: IV sodium bicarbonate, 1 ml/kg/hour for 6 hours after procedure.

% Female	43%
Mean age (SD)	median 74 (IQR 67-79)

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 106.96 (SD 26.52) umol/L % CKD 100% % Diabetes 25% % Hypertension 59% % ACEI 42%
Interventions	Contrast type iso-osmolar, non-ionic Contrast name Iodixanol Contrast dose, ml, mean (SD) median 160 (IQR 120-220) Contrast procedure coronary angiography

NAC + sodium chloride 0.9% (N = 252)

Pre-procedure: NAC given at a dose of 1200mg twice daily, on the day before and day of procedure, IV sodium chloride given at a dose of 1ml/kg/hour for 12 hours before procedure. Post-procedure: IV sodium chloride given at a dose of 1ml/kg/hour for 12 hours.

% Female	39%
Mean age (SD)	median 74;(IQR 70-79)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 106.08 (SD 26.52) umol/L % CKD 100% % Diabetes 23% % Hypertension 57% % ACEI 36%

	Interventions	Contrast type iso-osmolar, non-ionic Contrast name Iodixanol Contrast dose, ml, mean (SD) median 170 (IQR 120-230) Contrast procedure coronary angiography

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Maioli 2011

Bibliographic Reference	Maioli, Mauro; Toso, Anna; Leoncini, Mario; Micheletti, Carlo; Bellandi, Francesco; Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial; Circulation. Cardiovascular interventions; 2011; vol. 4 (no. 5); 456-62

Study details

Study location	Italy
Study setting	single centre
Study dates	July 2004 - December 2008
Duration of follow-up	72 hours
Sources of funding	none reported
Inclusion criteria	Age at least 18 years of age Other have had a STEMI and is a candidate for primary PCI
Exclusion criteria	Contrast contrast administered in previous 10 days History of dialysis end-stage renal failure requiring dialysis Did not provide consent
Sample size	461
Loss to follow-up	4 (3 did not have PCI, 1 had an emergency CABG)
Interventions	Contrast type non-ionic, dimeric iso-osmolar Contrast name Iodixanol Contrast dose, ml, mean (SD) 165.6 (SD 89.3) Contrast procedure PCI
Outcome measures	Contrast induced AKI

	at 48 and 72 hours: at 48 and 72 hours: defined as an increase in serum creatinine of at least 25% or 44umol/L over baseline Mortality in hospital mortality Renal failure need for RRT

Study arms

	Sodium bicarbonate (N = 150) Pre-procedure: sodium bicarbonate (154 mEq/L in dextrose and water) given as a bolus of 3 mL/kg of sodium bicarbonate solution in 1 hour, starting in the emergency room. Post-procedure: given as an infusion of 1 mL/kg per hour for 12 hours. Mean total volume: 1157 (SD 228) ml.

% Female	23.3%
Mean age (SD)	65 (SD 13) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 96 (SD 27) umol % Diabetes 20.7% % Hypertension 44%

	Sodium chloride 0.9% (N = 150) post-procedure only: given at a dose of 1ml/kg/hour for 12 hours after procedure.

% Female	27.3%
Mean age (SD)	66 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 97 (SD 35) umol/L % Diabetes 20.7% % Hypertension 47.3%

	no hydration (N = 150) unclear if no iv hydration only or no hydration at all
% Female	26.7%
Mean age (SD)	64 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 95 (SD 27) umol/L % Diabetes 22.7% % Hypertension 44.0%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Open label and unclear if allocation concealment; some differences between online protocol and study paper.)

Overall Directness

Directly applicable

Marenzi 2006

Bibliographic Reference	Marenzi G; Assanelli E; Marana I; Lauri G; Campodonico J; Grazi M; De Metrio M; Galli S; Fabbiocchi F; Montorsi P; Veglia F; Bartorelli AL; N-acetylcysteine and contrast-induced nephropathy in primary angioplasty.; The New England journal of medicine; 2006; vol. 354 (no. 26)

Study details

Study location	Italy
Study setting	Coronary care unit
Study dates	February 2003 - May 2005
Duration of follow-up	Length of hospital stay
Inclusion criteria	Other ST-segment elevation acute MI presented within 12h after onset (18h in case of cardiogenic shock)of symptoms
Exclusion criteria	Contrast known allergy to NAC Medications Long-term RRT
Sample size	354
Loss to follow-up	1 died during angioplasty
Interventions	Contrast type Non-ionic low osmolar Contrast name Iohexel Contrast procedure

	Echocardiogram within 24h of admission
Outcome measures	Contrast induced AKI at 48 and 72 hours Mortality in-hospital Renal failure need for RRT Serum creatinine clearance increase in serum creatinine of at least 25% at 72h over baseline

Study arms

IV NAC + IV sodium chloride 0.9% (N = 115)

Pre-procedure: single IV bolus Post-procedure: twice daily for 48 hours, 0.9% sodium chloride 1ml/kg/h IV for 12 hours

Duration of follow-up	During hospital stay
% Female	24.3%
Mean age (SD)	62.5 (SD 13) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) % Diabetes 13.9% % Hypertension 44.3% Notes 600mg
Interventions	Contrast type Non-ionic low osmolar Contrast name Iohexel Contrast dose, ml, mean (SD) 264 (SD 146) Contrast procedure Echocardiogram within 24h of admission

IV NAC + IV sodium chloride 0.9% (N = 118)

Pre-procedure: single IV bolus Post-procedure: twice daily for 48 hours, 0.9% sodium chloride 1ml/kg/h IV for 12 hours

% Female	18.5%
Mean age (SD)	62.6 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 93.7 (81.3 - 106.1) *median (IQR) % Diabetes 15.1% % Hypertension 41.2% Notes intervention dose 1200mg
Interventions	Contrast type Non-ionic low osmolar Contrast name Iohexel Contrast dose, ml, mean (SD) 253 (SD 108) Contrast procedure Echocardiogram within 24h of admission

IV sodium chloride (N = 119)

Pre-procedure: not reported Post-procedure: 0.9% sodium chloride 1ml/kg/h IV for 12 hours

% Female	18.5%
Mean age (SD)	62.6 (SD 12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) SD 93.7 (81.3 - 106.1) *median (IQR) % Diabetes 15.1%

		% Hypertension 41.2%
	Interventions	Contrast type Non-ionic low osmolar Contrast name Iohexel Contrast dose, ml, mean (SD) 274 (SD 113) Contrast procedure Echocardiogram within 24h of admission

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear if allocation concealment and some discrepancies between pre-registered protocol and results presented (although all relevant results were presented))

Overall Directness

Directly applicable

Martin-Moreno 2015

Bibliographic Reference	Martin-Moreno, Paloma L.; Varo, Nerea; Martinez-Anso, Eduardo; Martin-Calvo, Nerea; Sayon-Orea, Carmen; Bilbao, Jose I.; Garcia-Fernandez, Nuria; Comparison of Intravenous and Oral Hydration in the Prevention of Contrast-Induced Acute Kidney Injury in Low-Risk Patients: A Randomized Trial; Nephron; 2015; vol. 131 (no. 1); 51-8

Study details

Study location	Spain
Study setting	Hospital
Study dates	2008 - 2012
Duration of follow-up	24 hours
Sources of funding	This work was supported by grants from: Gobierno de Navarra, Departamento de Salud;and Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo FIS.
Inclusion criteria	Age ≥ 18 years eGFR ≥ 30 ml/min/1.73 m2 Other Hospitalised for at least 48 h
Exclusion criteria	Other conditions Diabetes mellitus, New York Heart Association class III–IV heart failure, acute exacerbations of chronic obstructive pulmonary disease Contrast Administration of iodinated contrast within the previous week; history of serious reactions to contrast media Medications Treatment with nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides and/or nephrotoxic chemotherapy) within the previous 48 h or within a few hours after contrast injection Blood pressure Resistant arterial hypertension defined as >150/90 mm Hg with antihypertensive treatment

	eGFR <30 ml/min/1.73 m 2 other Colonoscopy within the previous 48 h
Sample size	167
Loss to follow-up	37
Interventions	Contrast type Not reported Contrast name Iohexol Contrast dose, ml, mean (SD) Approximately 120 ml Contrast procedure Computed tomography
Outcome measures	Contrast induced AKI Serum creatinine of ≥ 25% from baseline within 24 h after contrast administration

Study arms

	IV sodium bicarbonate (N = 43) Pre-procedure: 1/6 molar 3 ml/kg/h, 1 hour pre-procedure Post-contrast: none

Sample size	51
Loss to follow-up	8
% Female	30.2
Mean age (SD)	59 (SD 15.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 79.56 (35.36) % ACEI 18.6 Notes NAC was given to 25.6% of participants

oral sodium citrate (N = 43)

Pre-contrast: 1,380 mg/l of sodium 75 ml/10 kg, divided into 4 doses (1 dose per hour), 4 hours pre-procedure Post-contrast: none

Sample size	54
Loss to follow-up	11
% Female	41.9
Mean age (SD)	56.6 (15.5)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 70.72 (26.52) % ACEI 16.3 Notes NAC was given to 23.2% of participants

no (intravenous) hydration (N = 44)

Pre-contrast: no prophylaxis for CI-AKI Post-contrast: none

Sample size	62
Loss to follow-up	18
% Female	41.0
Mean age (SD)	56.8 (16.8)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 79.56 (26.52) % ACEI 15.9 Notes NAC was given to 38.6% of participants

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Masuda 2007

Bibliographic Reference	Masuda M; Yamada T; Mine T; Morita T; Tamaki S; Tsukamoto Y; Okuda K; Iwasaki Y; Hori M; Fukunami M; Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure.; The American journal of cardiology; 2007; vol. 100 (no. 5); 781-786

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan

Study setting	Not reported
Study dates	April 2005 - June 2006
Duration of follow-up	2007 study: Follow-up of occurrence of contrast-induced neuropathy within 2 days of the procedure. Patients were followed up during hospitalisation to record clinical events 2008 study: Follow-up every 1 or 2 months for more than 1 year
Sources of funding	Not reported
Inclusion criteria	Age ≥20 years Other Renal dysfunction (serum creatinine concentration >1.1 mg/dl or estimated glomerular filtration rate <60 ml/min)
Exclusion criteria	Allergy Allergy to radiographic contrast media Contrast Recent exposure to radiographic contrast media within 2 days of study Medications Previous or planned administration of mannitol, fenoldopam, N-acetylcysteine or non-study sodium bicarbonate History of dialysis Pregnancy or breastfeeding Serum creatinine Change in concentration of ≥0.5 mg/dl during previous 24 hours
Sample size	61
Interventions	Contrast type Non-ionic, non-osmolality Contrast name Iopamidol (370 mg/dl) Contrast procedure Emergency diagnostic or interventional coronary procedure
Outcome measures	Contrast induced AKI Increase >0.5 mg/dl or >25% in serum creatinine concentration within 2 days of the procedure Mortality 2008 study Number of patients needing RRT Maintenance dialysis or kidney transplant

	Adverse events

Study arms

IV sodium bicarbonate (N = 31)

154 mEq/L sodium bicarbonate. 3 ml/kg/hour before the coronary procedure. 1 ml/kg/hour during and 6 hours after the procedure

Split between study groups	31
Loss to follow-up	1
% Female	37%
Mean age (SD)	75 (8)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 115.8 (45.9)* % Diabetes 27% % ACEI 50% Baseline eGFR, ml/min per 1.73m2, mean (SD) 40.2 (15.4)

IV sodium chloride 0.9% (N = 30)

154 mEq/L sodium chloride. 3 ml/kg/hour before the coronary procedure. 1 ml/kg/hour during and 6 hours after the procedure

Split between study groups	30
Loss to follow-up	1
% Female	41%
Mean age (SD)	76 (11)

	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 116.7 (57.5) % Diabetes 35% % ACEI 48% Baseline eGFR, ml/min per 1.73m2, mean (SD) 38.7 (15.4)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

High

(Unclear if allocation concealment, per protocol analysis, and trial stopped early for ethical reasons however, unclear if planned interim analysis and stopping rules)

Overall bias and Directness

Risk of bias judgement

High

(Unclear if allocation concealment, per protocol analysis, and trial stopped early for ethical reasons however, unclear if planned interim analysis and stopping rules.)

Overall Directness

Directly applicable

Masuda 2008

Bibliographic Reference	Masuda M; Yamada T; Okuyama Y; Morita T; Sanada S; Furukawa Y; Tsukamoto Y; Okuda K; Iwasaki Y; Yasui T; Fukunami M; Sodium bicarbonate improves long-term clinical outcomes compared with sodium chloride in patients with chronic kidney disease undergoing an emergent coronary procedure.; Circulation journal : official journal of the Japanese Circulation Society; 2008; vol. 72 (no. 10); 1610-1614

Study details

Study type	Associated study of another trial Masuda 2007

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(Unclear if allocation concealment, per protocol analysis, and trial stopped early for ethical reasons however, unclear if planned interim analysis and stopping rules.)

Overall Directness

Directly applicable

Merten 2004

Bibliographic Reference	Merten, Gregory J.; Burgess, W. Patrick; Gray, Lee V.; Holleman, Jeremiah H.; Roush, Timothy S.; Kowalchuk, Glen J.; Bersin, Robert M.; Van Moore, Arl; Simonton III, Charles A.; Rittase, Robert A.; Norton, H. James; Kennedy, Thomas P.; Prevention of Contrast-Induced Nephropathy With Sodium BicarbonateA Randomized Controlled Trial; JAMA; 2004; vol. 291 (no. 19); 2328-2334

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Single centre
Study dates	Sept 2002 to July 2003
Duration of follow-up	48 hours
Sources of funding	Carolinas medical centre who supplied contrast and fluids. No funding from manufacturers or suppliers.
Inclusion criteria	Serum creatinine Stable sCr ≥97.2µmol/l Age ≥18 years old
Exclusion criteria	Other conditions myeloma / pulmonary oedema Allergy allergy to radiocontrast Contrast exposure to contrast within 2 days of the study Medications administration of dopamine, mannitol, fenoldapam or NAC during the intended time of the study History of dialysis pre-existing RRT Pregnancy or breastfeeding Blood pressure

	uncontrolled hypertension Procedures Emergency catheterisation Serum creatinine sCr >707µmol/l or change in sCr ≥44.2µmol/l during the previous 24h
Sample size	119 out of 137 randomised
Split between study groups	Sodium chloride 0.9% - n=59 Sodium bicarbonate - n=60
Loss to follow-up	5 each arm excluded as no follow up laboratory tests, 4;each arm excluded for protocol violations.
Mean age (SD)	NR
Condition specific characteristics	% CKD 100%
Interventions	Intervention dose Sodium bicarbonate (154mEq/L in 5% dextrose and H2O) Intervention route IV Intervention pre-contrast 3ml/kg/h for 1h Intervention during contrast 1ml/kg/h during contrast Intervention post-contrast 1ml/kg/h for 6h post Contrast type low osmolar Contrast name iopamidol
Outcome measures	Contrast induced AKI CI-AKI at 48 hours (increase in sCr ≥25%) Mortality NR Number of patients needing RRT Adverse events No patients developed clinical heart failure or respiratory distress. One patient in the bicarbonate group had a blood pressure increase >30mmHG with the initial bolus, this responded to diuretics and patient did not develop CI-AKI or any other adverse events

	Length of hospital stay y “All individuals with CI-AKI experienced prolonged hospitalisation…”. No other information reported. Notes Change in MAP after initial bolus Urine pH after initial bolus Change in serum bicarbonate on day 1 Change in serum potassium on day 1 Change in serum Creatinine (highest level day 1or 2 used) Change in estimated GFR

Study arms

	Sodium bicarbonate (N = 60)	
	Sample size	60
	% Female	26.7%
	Mean age (SD)	66.7
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 167.1 (61.0) % CKD 100% % Diabetes 50% % Hypertension NR % ACEI NR % NSAIDs NR Baseline serum creatinine, mg/dl, median (IQR) NR Baseline eGFR, ml/min per 1.73m2, mean (SD) 41 (13)
	Interventions	Intervention dose Sodium bicarbonate (154mEq/L in 5% dextrose and H2O) Intervention route IV Intervention pre-contrast 3ml/kg/h for 1h

	Intervention during contrast 1ml/kg/h during contrast Intervention post-contrast 1ml/kg/h for 6h post Contrast type low osmolar Contrast name iopamidol Contrast dose, ml, mean (SD) 130 (72) Intervention (more details) For patients >110kg fluid was limited to that of a patient weighing 100kg Diuretics withheld on day of contrast

0.9% Sodium chloride (N = 59)

Sample size	59
% Female	23.7%
Mean age (SD)	69.2 (12) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 151.2 (37.1) % CKD 100% % Diabetes 76.3% % Hypertension NR % ACEI NR % NSAIDs NR Baseline eGFR, ml/min per 1.73m2, mean (SD) 45 (14)
Interventions	Intervention dose Sodium bicarbonate (154mEq/L in 5% dextrose and H2O) Intervention route IV

		Intervention pre-contrast 3ml/kg/h for 1h Intervention during contrast 1ml/kg/h during contrast Intervention post-contrast 1ml/kg/h for 6h post Contrast type low osmolar Contrast name iopamidol Contrast dose, ml, mean (SD) 134 (63)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness
Risk of bias judgement

Some concerns

(Trial terminated early but unclear if predefined stopping rules)

Overall Directness
Directly applicable

Miner 2004

Bibliographic Reference	Miner, Steven E.S.; Dzavik, Vladimir; Nguyen-Ho, Phong; Richardson, Robert; Mitchell, Jan; Atchison, Deborah; Seidelin, Peter; Daly, Paul; Ross, John; McLaughlin, Peter R.; Ing, Douglas; Lewycky, Peter; Barolet, Alan; Schwartz, Leonard; N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up; American Heart Journal; 2004; vol. 148 (no. 4); 690-695

Study details

Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Tertiary care
Study dates	March 2001 to October 2002
Duration of follow-up	3 days
Sources of funding	none reported
Inclusion criteria	Serum creatinine Patients without diabetes and a calculated creatinine clearance of <50 mL/min, Patients with diabetes and a calculated creatinine clearance of <100mL/min, Any patient with an absolute serum creatinine of > 200µmol/L Other previous diagnostic angiography undergoing planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI
Exclusion criteria	Other conditions Medications Ongoing need for IV nitroglycerin and treatment with NAC within 72 hrs of PCI History of dialysis dialysis or transplantation Pregnancy or breastfeeding Women of child-bearing age Blood pressure Baseline systolic blood pressure <80 mmHg

	Procedures Enrolment in another clinical trial Did not provide consent
Sample size	180
Loss to follow-up	25 in-hospital phase and 9 in long term follow up
Interventions	Contrast type low osmolar nonionic Contrast name Omnipaque Contrast dose, ml, mean (SD) not reported Contrast procedure planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI
Outcome measures	Contrast induced AKI at 48 hours, defined as planned PCI or urgent coronary angiography with high likelihood of ad hoc PCI. reduction in CI-AKI was limited to those patients enrolled the day prior to the procedure. Mortality in-hospital and at 6 months Number of patients needing RRT in-hospital and at 6 months

Study arms

	Oral NAC + sodum chloride 0.45% (N = 95) Pre-procedure: 2000mg oral NAC, first dose 8pm the night before the procedure with subsequent doses at 8am and 8pm the day of their procedure. Same day patients received their first dose at 8am and 8 pm on the same day. (prior day patients received a total of 6000mg and same day patients a total of 4000mg). IV sodium chloride 0.45% was given for 75ml/hour for 24 hours from the time of enrolment.

% Female	32%
Mean age (SD)	71 (SD8) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 124 (SD 49) umol/L % Diabetes 68% % Hypertension 72% % ACEI

IV sodium choride 0.45% (N = 85)

IV sodium chloride 0.45% was given for 75ml/hour for 24 hours from the time of enrolment.

% Female	34%
Mean age (SD)	69 (SD 11) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 130 (SD 58) umol/L % Diabetes 67% % Hypertension 77%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(Unclear how randomisation performed; unclear if allocation concealment; insufficient information in the protocol with regard to blinding procedures and any study dropouts; unclear how much participant data was used in the final analysis; unclear how proportion of missing data varied between study arms)

Overall Directness

Directly applicable

Mohamed 2008

Bibliographic Reference	Izani Wan Mohamed W; Darus, Z: Yusof Z; Oral N-acetylcysteine in prevention of contrast induced nephropathy following coronary angiogram; International Medical Journal; 2008; vol. 15 (no. 5); 353-361

Study details

Study type	Randomised controlled trial (RCT)
Study location	Malaysia
Study setting	Single hospital centre
Study dates	April 2006 to March 2007
Duration of follow-up	48 hours
Sources of funding	Research Department of University Sains Malaysia
Inclusion criteria	Serum creatinine creatinine clearance between 40 - 90 ml/min Age ≥18 years old

	received imaging elective admission for coronary angioplasty
Exclusion criteria	Other conditions Severe peptic ulcer disease; severe asthma Allergy allergy to NAC Pregnancy or breastfeeding Related conditions acute or reversible renal failure Serum creatinine Creatinine clearance less than 40 ml/min
Sample size	108
Loss to follow-up	8
Mean age (SD)	57 (7.5)
Interventions	Contrast type low osmolar, nonionic Contrast name iohexol (Omniplaque) Contrast procedure Coronary angiography
Outcome measures	Adverse events Need for dialysis CIN an increase in serum creatinine ≥ 25% from baseline

Study arms

	oral NAC + IV sodium chloride 0.45% (N = 53) oral NAC dose: 600 mg twice daily for four doses (mixed with orange drink), starting 12 hours prior to contrast administration (total oral NAC 1200mg daily for 2 days). IV sodium chloride 0.45% dose: 1 ml/kg/hr 12 hours before and after contrast administration
	Sample size: 53

Loss to follow-up	4
% Female	14.3
Mean age (SD)	57.6 (8.4)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 123.7 (17.08) % Diabetes 49 % Hypertension 91.8 % ACEI 81.6
Interventions	Contrast dose, ml, mean (SD) 136.73 (100.23)

IV sodium chloride 0.45% (N = 55)

IV sodium chloride 0.45% dose: 1 ml/kg/hr 12 hours before and after contrast administration

Sample size	55
Loss to follow-up	4
% Female	17.6
Mean age (SD)	56.4 (6.8)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 124.4 (21.9) % Diabetes 45.1 % Hypertension 90.2 % ACEI 74.5
Interventions	Contrast dose, ml, mean (SD)

		126.7 (94.4)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(>5% exclusions/missing outcomne data; unclear if allocation concealment)

Overall Directness

Directly applicable

Motohiro 2011

Bibliographic Reference	Motohiro M; Kamihata H; Tsujimoto S; Seno T; Manabe K; Isono T; Sutani Y; Yuasa F; Iwasaka T; A new protocol using sodium bicarbonate for the prevention of contrast-induced nephropathy in patients undergoing coronary angiography.; The American journal of cardiology; 2011; vol. 107 (no. 11)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	2 Japanese hospitals
Study dates	November 2004 - May 2007
Duration of follow-up	1 month
Sources of funding	none reported
Inclusion criteria	Age at least 20 years old eGFR <60ml/min/1.73m² Other undergoing coronary angiography or intervention
Exclusion criteria	Other conditions pulmonary oedema Allergy allergy to contrast Contrast exposure to radiographic contrast within in the previous 2 days Medications no patients received dopamine, mannitol, fenoldopam or NAC during intended study period History of dialysis Blood pressure uncontrolled hypertension (treated systolic blood pressure >160 mmHg or diastolic blood pressure > 100mmHg) Procedures emergency catheterization Serum creatinine sCr > 353.6 μmol/L or changes in sCr levels of ≥0.5mg/dl during the previous 24 hrs
Sample size	158
Loss to follow-up	3

Interventions	Contrast type low-osmolar, non-ionic Contrast name Iopamidol Contrast procedure coronary angiography or intervention
Outcome measures	Contrast induced AKI at 48 hours, defined as an Absolute increase in the sCr concentration of ≥44.2μmol/l* or as a 25% increase from the baseline value at 48 hrs after contrast exposure

Study arms

Sodium bicarbonate + sodium chloride 0.9% (N = 78)

Pre-contrast: Sodium bicarbonate (1000 mEq/L to 846ml of 5% dextrose in water) given at a dose of 1ml/kg/hour for 3 hours, with sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours pre-procedure. Post-procedure: Sodium bicarbonate (same dose as above) given for 6 hours and sodium chloride (same dose as above) for 12 hours.

% Female	25.3%
Mean age (SD)	71 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, μmol/l, mean (SD) 136.14 (SD 38.01) umol/L % Diabetes 56% % Hypertension 86% % ACEI 79%
Interventions	Contrast type low-osmolar, non-ionic Contrast name Iopamidol Contrast dose, ml, mean (SD) 140 (SD 50) ml Contrast procedure coronary angiography or intervention

Sodium chloride 0.9% (N = 77)

Pre-contrast: sodium chloride 0.9% given at a dose of 1ml/kg/hour for 12 hours pre-procedure. Post-procedure: sodium chloride (same dose as above) for 12 hours.

% Female	36%
Mean age (SD)	74 (SD 7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 137.02 (SD 38.90) umol/L % Diabetes 63% % Hypertension 83% % ACEI 90%
Interventions	Contrast type low-osmolar, non-ionic Contrast name Iopamidol Contrast dose, ml, mean (SD) 130 (SD 40) ml Contrast procedure coronary angiography or intervention

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if allocation concealment; unclear approach to intention to treat analysis; unblinded)

Overall Directness

Directly applicable

Mueller 2002

Bibliographic Reference	Mueller, Christian; Buerkle, Gerd; Buettner, Heinz J.; Petersen, Jens; Perruchoud, Andre P.; Eriksson, Urs; Marsch, Stephan; Roskamm, Helmut; Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty; Archives of internal medicine; 2002; vol. 162 (no. 3); 329-36

Study details

Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	Single University Hospital;
Study dates	April 1998 to May 1999
Duration of follow-up	48 hours
Sources of funding	None reported
Inclusion criteria	received imaging Elective or emergency coronary angioplasty

Exclusion criteria	Other conditions Cardiogenic shock; mechanical ventilation History of dialysis End stage renal failure with regular haemodialysis
Sample size	1620 randomised
Loss to follow-up	237
Interventions	Contrast type low-osmolar, nonionic Contrast name iopromide (Ultravist) and iomeprol (Imeron) Contrast procedure elective or emergency coronary angioplasty
Outcome measures	Mortality at 30 days Adverse events Major adverse cardiac events within 30 days, defined as death, myocardial infarction, urgent target vessel revascularisation, or hospitalisation for unstable angina; Peripheral vascular complications defined as false aneurysms requiring surgery, compression or bleeding requiring surgery or transfusion Length of hospital stay Need for dialysis during hospitalisation CIN an increase in serum creatinine concentration of at least 0.5 mg/dL (44 µmol/L) within 48 hours

Study arms

	IV sodium chloride 0.9% (N = 685) IV sodium chloride 0.9% dose: 154mmol/L at rate of 1ml/kg/h. From 8 am on day of procedure till 8am the following day (mean total fluid 2022ml).

Sample size	809
Loss to follow-up	124

% Female	26
Mean age (SD)	64 (IQR 63 - 65)
Condition specific characteristics	% CKD 20 % Diabetes 16 % Hypertension 65 Baseline serum creatinine, mg/dl, mean (SD) 0.92 (95%CI 0.90 - 0.94)
Interventions	Contrast dose, ml, mean (SD) 232 (95%CI 226 - 238)

IV sodium chloride 0.45% (N = 698)

IV sodium chloride 0.45% dose: in 5% glucose, 77mmol/L of sodium chloride at a rate of 1ml/kg/h. From 8 am on day of procedure till 8am the following day (mean total fluid: 2028ml).

Sample size	811
Loss to follow-up	113
% Female	25
Mean age (SD)	64 (95%CI 63 - 65)
Condition specific characteristics	% CKD 21 % Diabetes 16 % Hypertension 61 Baseline serum creatinine, mg/dl, mean (SD) 0.93 (95%CI 0.90 to 0.95)
Interventions	Contrast dose, ml, mean (SD) 236 (95%CI 229 to 243)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(large proportion of exclusions post-randomisation; Unclear how reasons for missing data varied between study arms; unclear of allocation concealment; non-blinded)

Overall Directness

Directly applicable

Nieto-Rios 2014

Bibliographic Reference	Nieto-Rios, John Fredy; Salazar, Wilmar Arley Maya; Sanchez, Oscar Mauricio Santos; Ortega, Janeth Liliana Jaramillo; Caro, Jorge Ignacio Garcia; Aristizabal, Julian Miguel Aristizabal; Higuita, Lina Maria Serna; Garcia, Alvaro Garcia; Barragan, Fabian Alberto Jaimes; Prevention of contrast induced nephropathy with sodium bicarbonate (the PROMEC study); Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia; 2014; vol. 36 (no. 3); 360-6

Study details

Study location	Colombia
Study setting	inpatients at Hospital Universitario San Vicente de Pauacute;l (Medellin, Colombia)
Study dates	May 1,;2007 - February 7, 2008
Duration of follow-up	Primary and secondary outcomes were evaluated and determined within 48 hours after administration of radiographic contrast.
Inclusion criteria	Serum creatinine serum creatinine ≥ 1.2 mg/dL (106.1 µmol/L) or type 2 Diabetes Mellitus. Age at least 18 years old received imaging scheduled to undergo tomography scan using contrast or angiography (included coronariography) with the nonionic radiographic contrast agent iohexol (640 mOsm/L, 647 mg of iohexol per milliliter)
Exclusion criteria	Other conditions current clinical diagnosis of exacerbated congestive heart failure, ejection fraction < 35% by previous echocardiography, signs of acute pulmonary edema within 48 hours before the procedure, requirement of an emergency procedure (e.g., aortography for diagnosis of aortic aneurism), patients with serum potassium < 3 mEq/L (because of the risk of hypokalemia induced by bicarbonate), or uncompensated diabetes mellitus (four different values > 200 mg/dL in the previous 24 hours) Allergy to contrast dye Contrast exposure to contrast 30 days prior to the study History of dialysis chronic renal disease with dialysis therapy or criteria for dialytic urgency Pregnancy or breastfeeding Blood pressure systolic blood pressure < 90 mmHg or requirement of vasopressors support Did not provide consent
Sample size	231
Loss to follow-up	11 never exposed to contrast dye.
Interventions	Contrast type nonionic radiographic contrast agent

	Contrast name Iohexol Contrast dose, ml, mean (SD) 640 mOsm/L, 647 mg of iohexol per milliliter Contrast procedure tomography scan using contrast or angiography
Outcome measures	Serum creatinine clearance change in serum creatinine CIN Development of CIN: defined by an increase in serum creatinine of 25% or more within 2 days after administration of the radiographic contrast, and development of complications as I) superficial phlebitis: presence of inflammatory signs on the route of the vein where the infusion was administrated; II) hypokalemia: serum potassium < 3 mEq/L; III) metabolic alkalosis: arterial pH > 7.45 with serum bicarbonate > 24 mEq/L; and IV) decompensated heart failure: signs of volume overload requiring a therapeutic intervention to resolve them.

Study arms

IV sodium chloride 0.9% (N = 112)

1 ml/ kg/hour of 0.9% saline infusion (154 mEq/L) starting 12 hours before and continuing 12 hours after iohexol contrast exposition

% Female	31.6%
Mean age (SD)	59.8 (17.2)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 116.7 (SD 28.3) umol/L % Diabetes 19.5% % Hypertension 59.3%

IV sodium bicarbonate (N = 100)

Pre-procedure: 3 ml/kg of sodium bicarbonate solution (150 mEq/L) during one hour prior. Post-procedure: 1 ml/kg/hour for 6 hours.

% Female	43%

	Mean age (SD)	60.7 (SD 17.1) years
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 114.9 (SD 35.4) umol/L % Diabetes 22.4% % Hypertension 51.4%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Nijssen 2017

Bibliographic Reference	Nijssen, Estelle C.; Rennenberg, Roger J.; Nelemans, Patty J.; Essers, Brigitte A.; Janssen, Marga M.; Vermeeren, Marja A.; Ommen, Vincent van; Wildberger, Joachim E.; Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial; Lancet (London, England); 2017; vol. 389 (no. 10076); 1312-1322

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Maastricht University Medical Centre
Study dates	June 17, 2014 -;July 17, 2016
Duration of follow-up	up to 35 days following procedure.
Sources of funding	none reported
Inclusion criteria	Age at least 18 years of age eGFR estimated glomerular filtration rate (eGFR) between 45 and 59 mL per min/1·73 m² combined with either diabetes, or at least two predefined risk factors (age >75 years; anaemia defined as haematocrit values <0·39 L/L for men, and <0·36 L/L for women; cardiovascular disease; non-steroidal anti-inflammatory drug or diuretic nephrotoxic medication); or eGFR between 30 and 45 mL per min/1·73 m²; or multiple myeloma or lymphoplasmacytic lymphoma with small chain proteinuria.
Exclusion criteria	Medications taking renal replacement therapy Procedures emergency procedures, intensive care patients, known inability to plan primary endpoint data collection, no referral for prophylactic hydration, participation in another randomised trial, and isolation (infection control) Did not provide consent eGFR <30 mL/min/1.73m2
Sample size	660
Loss to follow-up	all included in safety endpoint analyses; 140 were not included in the 26-35 day analysis of renal function.

Interventions	Contrast type non-ionic, monomeric, low-osmolar iodinated contrast medium Contrast name Ultravist Contrast dose, ml, mean (SD) 300mg iodine per ml Contrast procedure CT scan
Outcome measures	Adverse events Major adverse events were defined as all-cause mortality, renal replacement therapy, intensive care admission, and sequelae of fluid administration. Major renal adverse events were defined as renal failure (defined as eGFR <15 mL per min/1·73 m²), renal decline with >10 eGFR units, renal decline to eGFR lower than 30 mL per min/1·73 m², or a combination of the latter two, at 26–35 days. Clinical sequelae of fluid administration included symptomatic heart failure, hypernatraemia or hyponatraemia, and supraventricular or ventricular arrhythmias. Serum creatinine clearance mean change in serum creatinine from baseline at 2–6 and 26–35 days after contrast administration CIN defined as the between-group difference in proportion of patients with an increase in serum creatinine by more than 25% or 44 µmol/L23 within 2–6 days of contrast exposure, and costeffectiveness of no prophylaxis compared with intravenous prophylactic hydration in the prevention of contrast-induced nephropathy.

Study arms

	IV sodium chloride 0.9% (N = 328) Pre-procedure: prophylactic intravenous 0·9% NaCl 3–4 mL/kg per hour during 4 h before. Post-procedure: same again, for 4 hours. When deemed necessary, the physician could choose to instead administer long protocol intravenous 0·9% NaCl 1 mL/kg per h during 12 h before and 12 h after contrast administration.

% Female	41%
Mean age (SD)	71.9 (SD 9.3) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 118.78 (SD 27.63) % Diabetes 32%

	% NSAIDs 48% Baseline eGFR, ml/min per 1.73m2, mean (SD) 47.59 (SD 8.01)

no hydration (N = 332)

no prophylactic hydration given

% Female	36%
Mean age (SD)	72.6 (SD 9.3) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 117.71 (SD 24.62) umol/L % Diabetes 33% % NSAIDs 49% Baseline eGFR, ml/min per 1.73m2, mean (SD) 47.59 (SD 8.01)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(though a significant amount of missing outcome data)

Overall Directness

Directly applicable

Oldemeyer 2003

Bibliographic Reference	Oldemeyer, J.Bradley; Biddle, W.Paul; Wurdeman, Richard L; Mooss, Aryan N; Cichowski, Erica; Hilleman, Daniel E; Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography; American Heart Journal; 2003; vol. 146 (no. 6); 1089-1094

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital inpatient
Duration of follow-up	48 hours
Sources of funding	none reported
Inclusion criteria	Serum creatinine baseline calculated creatinine clearance <50ml/min; Serum creatinine >1.2mg/dl Age at least 19 years of age Other referred for elective coronary angiography; anticipated use of at least 75ml of contrast.
Exclusion criteria	Other conditions cardiogenic shock or emergent angiography.

	Allergy known allergy to contrast or acetylcysteine. Medications administration of mannitol, IV catecholamines, diuretics, theophylline, or contrast agent within 7 days of study entry. History of dialysis undergoing dialysis Related conditions unstable renal function as evidence by change in serum creatinine of at least 0.5mg/dl or at least 25% in prior 10 days. Procedures mechanical ventilation
Sample size	96
Loss to follow-up	none reported
Interventions	Contrast type low osmolar, non-ionic Contrast name Isovue Contrast dose, ml, mean (SD) 0.76 mg/ml, 370 mg iodine/ml Contrast procedure coronary angiography
Outcome measures	Contrast induced AKI at 48 hours, absolute increase in serum creatinine of ≥0.5mg/dl or a relative increase of ≥25% in serum creatinine compared to baseline Length of hospital stay Renal failure need for RRT

Study arms

	oral NAC + IV sodium chloride 0.45% (N = 49) Pre-procedure: 1500mg NAC given orally in 120 ml of carbonated beverage, using the 10% acetylcysteine inhalation solution starting the evening before angiography and every 12 hours for 4 doses. IV 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours. Post-procedure: 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.

% Female	44%
Mean age (SD)	77 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 144.09 (SD 71.60) umol/L % Diabetes 41% % Hypertension 69%

IV sodium chloride 0.45% (N = 47)

Pre-procedure: 1IV 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.
Post-procedure: 0.45% sodium chloride given at a dose of 1ml/kg for 12 hours.

% Female	41%
Mean age (SD)	75 (SD8) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 146.74 (SD 57.46) % Diabetes 49% % Hypertension 74%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Primarily "some concerns" because it was unclear if there were any exclusions post-randomisation; unclear approach to analysis; unclear if allocation concealment)

Overall Directness

Directly applicable

Poletti 2007

Bibliographic Reference	Poletti PA; Saudan P; Platon A; Mermillod B; Sautter AM; Vermeulen B; Sarasin FP; Becker CD; Martin PY; I.v. N-acetylcysteine and emergency CT: use of serum creatinine and cystatin C as markers of radiocontrast nephrotoxicity.; AJR. American journal of roentgenology; 2007; vol. 189 (no. 3)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	Inpatient hospital emergency department
Duration of follow-up	4 days
Sources of funding	supported by grant for research and development by the University hospital of Geneva
Inclusion criteria	Serum creatinine Serum Cr >106 umol/L received imaging emergency CT needed within 12 hours of admission

Exclusion criteria	Other conditions end-stage renal failure necessitating dialysis, suspicion of acute renal obstruction, asthma, severe cardiac failure or hemodynamically unstable condition contraindicating IV hydration Pregnancy or breastfeeding
Sample size	87
Loss to follow-up	7
Interventions	Contrast type nonionic low-osmolality iodine contrast Contrast name iopromide Contrast dose, ml, mean (SD) bolus of 2ml/kg and a standard dose of 100ml for brain imaging or suspicion of PE Contrast procedure CT scan
Outcome measures	Contrast induced AKI at least 25% increase in serum Cr over baseline

Study arms

	IV NAC + IV sodium chloride 0.45% (N = 44) Pre-contrast: 900mg of NAC diluted in a 50ml solution of 5% glucose, with 0.45% sodium chloride given at a dose of 5ml/kg for 1 hour. Post-contrast: 900 mg NAC minxued into 0.45% sodium chloride perfusion at a dose of 1ml/kg/hour for 12 hours

% Female	41%
Mean age (SD)	69.5 (SD 18.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 146 (SD 35) umol/L % Diabetes 18% % ACEI 10% % NSAIDs

	22%

IV sodium chloride 0.45% (N = 43)

Pre-contrast: 0.45% sodium chloride given at a dose of 5ml/kg for 1 hour. Post-contrast: 0.45% sodium chloride perfusion at a dose of 1ml/kg/hour for 12 hours

% Female	33%
Mean age (SD)	72.7 (SD 17.2) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 148 (SD 36) umol/L % Diabetes 12% % ACEI 24% % NSAIDs 10%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear randomisation process; unclear if allocation concealment; unclear pre-planned approach to missing data.)

Overall Directness

Directly applicable

Rashid 2004

Bibliographic Reference	Rashid ST; Salman M; Myint F; Baker DM; Agarwal S; Sweny P; Hamilton G; Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine.; Journal of vascular surgery; 2004; vol. 40 (no. 6)

Study details

Study location	UK
Study setting	Tertiary centre - vascular surgery department
Study dates	unclear
Duration of follow-up	up to 7 days
Sources of funding	none reported
Inclusion criteria	Serum creatinine subgroup analysis also presented for normal vs. raised serum creatinine Other patients with vascular disease undergoing elective angiography or angioplasty
Sample size	94
Loss to follow-up	9 drop outs after randomisation
Interventions	Contrast type low-osmolar

	Contrast name Iohexol (omnipaque) Contrast dose, ml, mean (SD) 143.2 (SD 69.4) Contrast procedure angiography or angioplasty
Outcome measures	Contrast induced AKI at 48 hours: defined as increase in serum creatine of 44.2 umol/L or 25% over baseline Mortality at 7 days Renal failure requiring RRT

Study arms

IV NAC + IV sodium chloride 0.9% (N = 46)

IV NAC: 1000mg IV given in the bag of sodium chloride 0.9% pre and post procedure. Sodium chloride: 0.9% 500ml given 6-12 hours pre-procedure given for 4-6 hours and immediately post-procedure for 4-6 hours.

% Female	41.3%
Mean age (SD)	72.1 (SD 12.3) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 109.9 (SD 41.2) % CKD 37.0% % Diabetes 37.0%

IV sodium chloride (N = 48)

Sodium chloride: 0.9% 500ml given 6-12 hours pre-procedure given for 4-6 hours and immediately post-procedure for 4-6 hours.

% Female	31.25%

	Mean age (SD)	68.8 (SD 12.3) years
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 124.3 (SD 63.5) % CKD 43.8% % Diabetes 27.1%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear predefined approach to missing data, unclear how randomisation was performed)

Overall Directness

Directly applicable

Reinecke 2007

Bibliographic Reference	Reinecke H; Fobker M; Wellmann J; Becke B; Fleiter J; Heitmeyer C; Breithardt G; Hense HW; Schaefer RM; A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) Trial.; Clinical research in cardiology : official journal of the German Cardiac Society; 2007; vol. 96 (no. 3); 130-139

Study details

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Single centre
Study dates	January 2001 - July 2004
Duration of follow-up	up to 60 days
Sources of funding	supported by an unrestricted research grant to the hospital of the University of Muenster from Schering AG
Inclusion criteria	Serum creatinine sCr 114.9 - 309.4 umol/L Other admitted for elective left heart catheterization
Exclusion criteria	Other conditions acute or recent (<30 days) MI, congestive heart failure, recipient of transplanted organs, Contrast previous contrast medium <7 days Procedures monoclonal gammopathy
Sample size	424 (extracted for this review)
Loss to follow-up	121 did not return questionnaire assessing adverse events; 60 did not have sCr levels measured at 72 hours. ;
Interventions	Contrast type non-ionic, iso-osmolar Contrast name Ioproimde Contrast procedure

	Coronary angiography
Outcome measures	Contrast induced AKI at 24 and 72 hours, and at 30-60 days; defined as an increase in enzymaticaly determined sCr of at least 44.2 umol/L Mortality in-hospital and 30 day mortality Adverse events relevant bleeding (loss in hemoglobin of 2g/dl or more) Renal failure in-hospital haemodialysis due to oliguria or uremia

Study arms

Oral NAC + sodium chloride 0.9% (N = 146)

Pre-procedure: 600mg oral NAC one dose the evening before procedure and another dose the morning before procedure, IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours Post-procedure: one dose the evening after procedure and another dose the morning the day after procedure, IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours

% Female	17.1
Mean age (SD)	66.7 (SD 10.1) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 132.6 (IQR 114.9 - 168.0) % Diabetes 31.5% % Hypertension 74.7%
Interventions	Contrast type non-ionic, iso-osmolar Contrast name Ioproimde Contrast dose, ml, mean (SD) contrast dye 197 (SD 80) mg/dl Contrast procedure Coronary angiography

Sodium chloride 0.9% (N = 140)

Pre-procedure: IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours Post-procedure: IV sodium chloride 0.9% (500 ml 5% glucose and 500 ml sodium chloride) given for 12 hours

% Female	17.1%
Mean age (SD)	66.7 (SD 10.6) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 123.8 (IQR 114.9 -168.0) % Diabetes 28.6% % Hypertension 77.9%
Interventions	Contrast type non-ionic, iso-osmolar Contrast name Ioproimde Contrast dose, ml, mean (SD) contrast dye 118 (SD 79) mg/dl Contrast procedure Coronary angiography

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(Unclear randomisation process, unclear if allocation concealment, physicians had preconceived ideas about superiority of certain interventions, this led to significant cross-over of treatment between arms.)

Overall Directness

Directly applicable

Sadineni 2017

Bibliographic Reference	Sadineni, R.; Karthik, K. R.; Swarnalatha, G.; Das, U.; Taduri, G.; N-acetyl cysteine versus allopurinol in the prevention of contrast nephropathy in patients with chronic kidney disease: A randomized controlled trial; Indian journal of nephrology; 2017; vol. 27 (no. 2); 93-98

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Single hospital centre
Study dates	June to December 2015
Duration of follow-up	48 hours
Sources of funding	None
Inclusion criteria	Serum creatinine ≥1.2 mg/dl on most recent sample drawn within 3 months of planned procedure Age

	>30 years old received imaging Patients undergoing clinically driven nonemergent coronary angiography and percutaneous coronary interventions for both stable and unstable patients with angina, non-ST-segment elevation myocardial infarction (NSTEMI) and acute myocardial infarction/STEMI
Exclusion criteria	Other conditions cardiogenic shock, pulmonary edema, mechanical ventilator Allergy history of hypersensitivity reaction to contrast media Contrast ntravascular administration of contrast material within previous 6 days Medications parenteral use of diuretics, recent use of NAC, recent use of ascorbic acid, and use of metformin or NSAIDS within 48 h of procedure History of dialysis endstage renal disease requiring dialysis, Pregnancy or breastfeeding Related conditions acute renal failure Procedures emergent coronary angiography
Sample size	95
Loss to follow-up	none declared
Interventions	Contrast type iso-osmolar, non-ionic Contrast name iodixanol (Visipaque) Contrast procedure nonemergent coronary angiography and percutaneous coronary interventions
Outcome measures	Mortality Need for dialysis CIN either a relative increase in serum creatinine from baseline of ≥25% or an absolute increase of ≥0.3 mg/dl (44.2 µmol/L) during days 1 and 2 post-contrast

Study arms

oral NAC + IV sodium chloride 0.9% (N = 35)

oral NAC dose: 600 mg twice daily. one day before and after the procedure (total 1200mg daily for two days). IV sodium chloride 0.9%: 0.5 ml/kg/h. 12 hours before and 12 hours after the procedure.

% Female	22.9
Mean age (SD)	60.7 (10.6)
Condition specific characteristics	% Diabetes 62.9 % Hypertension 88.6 Baseline serum creatinine, mg/dl, mean (SD) 2.2 (0.9)
Interventions	Contrast dose, ml, mean (SD) 61.4 (34.8)

IV sodium chloride 0.9% (N = 30)

IV sodium chloride 0.9%: 0.5 ml/kg/h. 12 hours before and 12 hours after the procedure.

% Female	13.3
Mean age (SD)	62.6 (11.8)
Condition specific characteristics	% Diabetes 63.3 % Hypertension 86.7 Baseline serum creatinine, mg/dl, mean (SD) 2.19 (1.01)
Interventions	Contrast dose, ml, mean (SD) 77.3 (43.3)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(Unclear how randomisation was performed; unclear if allocation concealment; unclear if significant differences between groups at baseline; unclear if blinding used; unclear if appropriate analysis used to investigate effect of assignment to intervention; unclear if participants excluded or missing data post-randomisation, unclear how results were analysed.)

Overall Directness

Directly applicable

Saitoh 2011

Bibliographic Reference	Saitoh T; Satoh H; Nobuhara M; Machii M; Tanaka T; Ohtani H; Saotome M; Urushida T; Katoh H; Hayashi H; Intravenous glutathione prevents renal oxidative stress after coronary angiography more effectively than oral N-acetylcysteine.; Heart and vessels; 2011; vol. 26 (no. 5); 465-472

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan

Study setting	University School of Medicine
Study dates	From September 2006 to March 2008
Duration of follow-up	48h
Sources of funding	Not reported
Inclusion criteria	Serum creatinine serum creatinine ≥1.5 mg/dl and/or creatinine clearance <60 ml/min
Sample size	14
Interventions	Contrast type low-osmolar Contrast name iomeprol (Iomeron) Contrast procedure elective diagnostic CAG Intervention (more details) This RCT included a third arm with glutathione + IV sodium chloride 0.9% but glutathione was not relevant for this review
Outcome measures	Contrast induced AKI increase in serum creatinine level by at least 0.5 mg/dl and/or 25%

Study arms

oral NAC + IV sodium chloride 0.9% (N = 7)

Pre-contrast: oral NAC 704 mg twice daily 1 day before CAG for a total of 2 days, with IV sodium chloride 0.9% 1 ml/kg/h 12 h before the administration of contrast.
Post-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h after CAG.

Loss to follow-up	None
% Female	14
Mean age (SD)	72.1 (2.7)

Condition specific characteristics	% ACEI ACEI/ARB 71
Interventions	Contrast dose, ml, mean (SD) 117.1 (9.0)

IV sodium chloride 0.9% (N = 7)

Pre-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h before the administration of contrast. Post-contrast: IV sodium chloride 0.9% 1 ml/kg/h 12 h after CAG.

Loss to follow-up	None
% Female	14
Mean age (SD)	76.5 (2.8)
Condition specific characteristics	% ACEI ACEI/ARB 43
Interventions	Contrast dose, ml, mean (SD) 113.6 (14.5)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(unclear if allocation concealment; no protocol cited)

Overall Directness

Directly applicable

Seyon 2007

Bibliographic Reference	Seyon RA; Jensen LA; Ferguson IA; Williams RG; Efficacy of N-acetylcysteine and hydration versus placebo and hydration in decreasing contrast-induced renal dysfunction in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention.; Heart & lung : the journal of critical care; 2007; vol. 36 (no. 3); 195-204

Study details

Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	24 and 48 hours after coronary angiography
Sources of funding	Not reported
Inclusion criteria	Serum creatinine Baseline ≥115 µmol/l (1.4 mg/dL) for males or equal to or greater than 115 mol/L (1.3 mg/dL) for females Age ≥18 years Other

	Diagnosis of acute coronary syndrome, scheduled for coronary angiography with or without concomitant PCI; Creatine clearance less than 50 ml/min
Exclusion criteria	Allergy known sensitivity to N-acetylcysteine Medications Current treatment with theophylline or mannitol, dialysis therapy Pregnancy or breastfeeding Blood pressure systolic <90 mm Hg requiring inotropic support other Acute gastrointestinal disorder; Deemed by cardiologist to be unsuitable to receive intravenous hydration therapy
Sample size	40
Outcome measures	Contrast induced AKI Absolute increase in serum creatinine of 44 mol/L (.5 mg/dL) within 48 hours of contrast media exposure and/or a relative increase in serum creatinine of 25% above baseline within 48 hours of contrast media exposure

Study arms

Oral NAC + IV sodium chloride 0.45% (N = 20)

NAC: 600 mg four times daily. First dose at 8 am the day of the procedure and 3 doses after coronary angiography with the first dose at 8 pm Sodium chloride 0.45%: 1 ml/kg/hour

Split between study groups	20
Loss to follow-up	0
% Female	40%
Mean age (SD)	76.4 (5.9)
Condition specific characteristics	% Diabetes 40% % Hypertension 55%

Placebo + IV sodium chloride 0.45% (N = 20)

Placebo: Four times daily. First dose at 8 am the day of the procedure and 3 doses after coronary angiography with the first dose at 8 pm Sodium chloride 0.45%: 1 ml/kg/hour

Split between study groups	20
Loss to follow-up	0
% Female	30%
Mean age (SD)	74.7 (9.7)
Condition specific characteristics	% Diabetes 40% % Hypertension 60%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear how randomisation performed, unclear if allocation concealment; trial terminated early without clear stopping rules.)

Overall Directness

Directly applicable

Shyu 2002

Bibliographic Reference	Shyu KG; Cheng JJ; Kuan P; Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure.; Journal of the American College of Cardiology; 2002; vol. 40 (no. 8)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	clinical centre
Duration of follow-up	48 hours
Sources of funding	Funded by the research committee of Shin Kong Wu Ho-Su memorial Hospital
Inclusion criteria	Serum creatinine Serum creatinine >176.8 µmol/l and <530.4 µmol/l; Rates of creatinine clearance < 40 ml/min and >8 ml/min; history of chronic renal failure with a stable serum creatinine concentrations (A difference of ≤0.1 mg/dl between baseline serum creatinine at 12 -24 hrs before coronary angiography and serum creatinine measured 1-2 weeks before angiography)
Exclusion criteria	Other conditions Acute MI requiring primary or rescue coronary intervention, cardiogenic shock Allergy Allergy to study medications Medications Use of vasopressors before the procedure History of dialysis

	Current peritoneal dialysis or hemodialysis; Planned post contrast dialysis
Sample size	121
Condition specific characteristics	% Hypertension 70%
Interventions	Contrast type nonionic, low-osmolar Contrast name Iopamidol (Iopamiro) Contrast dose, ml, mean (SD) decided by each patients cardiologist ipamidol content was 0.755 mg/ml and iodine content was 370 mg/ml Contrast procedure cardiac angiography
Outcome measures	Contrast induced AKI at 48 hours, increase in serum creatinine of at least 44.2 µmol/l at 48 hrs after contrast

Study arms

Oral NAC + sodium chloride 0.45% (N = 60)

Pre-procedure: 400mg NAC twice daily for a day prior to and day of procedure. IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure.

% Female	30%
Mean age (SD)	70 (SD 7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 247.52 (SD 70.72) umol/L % Diabetes 63% % Hypertension 70% % ACEI 40%

	sodium chloride 0.45% (N = 61) Pre-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure.

% Female	34.4%
Mean age (SD)	70 (SD 7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 247.52 (70.72) umol/L % Diabetes 64% % Hypertension 67% % ACEI 43%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(No description of randomisation process or if allocation concealment; no approach to missing data described.)

Overall Directness

Directly applicable

Solomon 2015

Bibliographic Reference	Solomon, Richard; Gordon, Paul; Manoukian, Steven V.; Abbott, J. Dawn; Kereiakes, Dean J.; Jeremias, Allen; Kim, Michael; Dauerman, Harold L.; Investigators, Boss Trial; Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD; Clinical journal of the American Society of Nephrology : CJASN; 2015; vol. 10 (no. 9); 1519-24

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	22;centres
Study dates	March 2010 - May 2012
Duration of follow-up	6 months
Sources of funding	Supported by Sci inc.
Inclusion criteria	Age at least 18 years old eGFR <45 ml/min per 1.73m2 Other scheduled for elective coronary or peripheral angiography
Exclusion criteria	Other conditions haemodynamic instability, hypocalcemia

	History of dialysis "RRT" Did not provide consent
Sample size	391
Loss to follow-up	23 did not receive either investigational product or contrast
Interventions	Contrast type choice of contrast agent were left to individual participating sites Contrast procedure angiography Intervention (more details) for both arms, post-procedure infusion could be extended to 5 hours in people with a history of congestive heart failure, or significant edema.
Outcome measures	Contrast induced AKI at 72 hours, defined as increase in sCr of at least 44.2 umol/L or 25% over baseline Mortality and time to death, up to 6 months Length of hospital stay Renal failure need for RRT Composite outcome first occurrence of death, RRT, or a reduction in eGFR of at least 20% confirmed by at least 2 separate measurements between days 30 and day 180

Study arms

	Sodium bicarbonate (N = 195) Pre-procedure: 1.3% sodium bicarbonate (154 mEq/L) given at 5ml/kg over 1 hour. post-procedure: 1.5 ml/kg per h during and for 4 h after angiography

% Female	43%
Mean age (SD)	72;(SD 10);years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 175.0 (SD 54.8) umol/L % Diabetes

	63% % Hypertension 94% Baseline eGFR, ml/min per 1.73m2, mean (SD) 31.7 (SD 7.7)
Interventions	Contrast type choice of contrast agent were left to individual participating sites Contrast dose, ml, mean (SD) 110 (SD 66) ml Contrast procedure angiography Intervention (more details) for both arms, post-procedure infusion could be extended to 5 hours in people with a history of congestive heart failure, or significant edema.

Sodium chloride 0.9% (N = 196)

Pre-procedure: 154 mEq/L sodium chloride 0.9% given at 5ml/kg over 1 hour. post-procedure: 1.5 ml/kg per h during and for 4 h after angiography

% Female	42%
Mean age (SD)	72 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 163.5 (SD 43.3) umol/L % Diabetes 55% % Hypertension 94% Baseline eGFR, ml/min per 1.73m2, mean (SD) 33.8 (SD 7.3)
Interventions	Contrast type choice of contrast agent were left to individual participating sites Contrast dose, ml, mean (SD) 104 (SD 72) ml Contrast procedure angiography Intervention (more details)

		for both arms, post-procedure infusion could be extended to 5 hours in people with a history of congestive heart failure, or significant edema.

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Tamura 2009

Bibliographic Reference	Tamura, Akira; Goto, Yukie; Miyamoto, Kumie; Naono, Shigeru; Kawano, Yoshiyuki; Kotoku, Munenori; Watanabe, Toru; Kadota, Junichi; Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure; The American journal of cardiology; 2009; vol. 104 (no. 7); 921-5

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	2 Japanese hospitals
Duration of follow-up	7 days
Sources of funding	none reported
Inclusion criteria	Serum creatinine sCr >97.24 to <176.8 umol/L Age >20 years old Other scheduled for elective coronary arteriography or percutaneous coronary intervention
Exclusion criteria	Other conditions ACS within the proceeding 1 month, Serve symptoms of heart failure (New York heart association functional class IV), Left ventricular ejection fraction < 25%, Severe chronic respiratory disease, Single functioning kidney Allergy allergy to contrast Contrast Exposure to contrast medium within the previous 48 hrs Medications Administration of dopamine, theophylline, mannitol, fenoldopam or NAC History of dialysis Pregnancy or breastfeeding
Sample size	144
Loss to follow-up	0
Interventions	Contrast type low-osmolar, non-ionic Contrast name Iohexel Contrast procedure arteriography or PCI

	Intervention (more details) Saline hydration: for patients >80kg infusion rate was limited to 80 ml/hr (40 ml/hr for patients with left ventricular ejection fraction < 40%) Diuretics were routinely held on the day of the procedure and the decision as to when diuretics were restarted was left to the discretion of the attending physician
Outcome measures	Contrast induced AKI at 72 hours defined as increase in sCr of >44.2umol/L or >25% increase from baseline. Mortality at 7 days Renal failure need for RRT

Study arms

	Sodium bicarbonate + sodium chloride 0.9% (N = 72) Pre-procedure: sodium bicarbonate given as a single 20mEq IV bolus, 5 minutes before contrast. Sodium chloride 0.9% given at a dose of 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) for 12 hours prior to contrast procedure. Post-procedure: Sodium chloride 0.9% (same dose as pre-procedure) for 12 hours.

% Female	16.7%
Mean age (SD)	72.3 SD 9.9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 120.22 (SD15.91) umol/L % Diabetes 59.7% % Hypertension 84.7% % ACEI 25%
Interventions	Contrast type low-osmolar, non-ionic Contrast name Iohexel Contrast dose, ml, mean (SD) 82.1 (SD 40.4) ml

	Contrast procedure arteriography or PCI

Sodium chloride 0.9% (N = 72)

Pre-procedure: Sodium chloride 0.9% given at a dose of 1 mL/kg/hr (0.5 ml/kg/hr for patients with left ventricular ejection fraction <40%) for 12 hours prior to contrast procedure. Post-procedure: Sodium chloride 0.9% (same dose as pre-procedure) for 12 hours.

% Female	8.3%
Mean age (SD)	73.3 (SD 7.7) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 121.99 (SD 16.80) umol/L % Diabetes 56.9% % Hypertension 83.3% % ACEI 16.7% % NSAIDs 0%
Interventions	Contrast type low-osmolar, non-ionic Contrast name Iohexel Contrast dose, ml, mean (SD) 87.8 (SD44.9) ml Contrast procedure arteriography or PCI

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(although unclear if allocation concealment)

Overall Directness

Directly applicable

Tepel 2000

Bibliographic Reference	Tepel M; van der Giet M; Schwarzfeld C; Laufer U; Liermann D; Zidek W; Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine.; The New England journal of medicine; 2000; vol. 343 (no. 3)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Inpatient
Duration of follow-up	6 days
Sources of funding	none reported

Inclusion criteria	Serum creatinine sCr > 106 µmol/L; CrCl < 50ml/min; also need to have a history of chronic renal failure and with stable serum creatinine concentrations. Other underwent elective CT for the evaluation of an abdominal or thoracic illness.
Exclusion criteria	Other conditions acute renal failure
Sample size	83
Loss to follow-up	0
Interventions	Contrast type non-ionic low-osmolar Contrast name opromide Contrast dose, ml, mean (SD) 75 ml infusion contained 0.623 g of iopromide per ml, and the iodine content was 300 mg per ml Contrast procedure elective CT
Outcome measures	Contrast induced AKI at 48 hours, defined as an increase in the serum creatinine 0.5 mg per deciliter 48 hours after administration of the contrast agent Number of patients needing RRT

Study arms

	Oral NAC plus sodium chloride 0.45% (N = 41) Pre-procedure: 600mg NAC given twice daily, day before and on the day of administration of the contrast agent. IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours.

% Female	41.5%
Mean age (SD)	66 (SD 11) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 221 (SD 114.92) umol/L % Diabetes 32% % ACEI 20%

Sodium chloride 0.45% (N = 42)

Pre-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours prior to procedure. Post-procedure: IV sodium chloride 0.45% given at a dose of 1ml/kg/hour for 12 hours.

% Female	45.2%
Mean age (SD)	65 (SD 15) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 212.16 (SD 114.92) % Diabetes 33% % ACEI 12%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness
Risk of bias judgement

Some concerns

(Unclear if allocation concealment; unclear approach to randomisation; unclear if blinded; unclear approach to missing outcome data)

Overall Directness

Directly applicable

Thiele 2010

Bibliographic Reference	Thiele H; Hildebrand L; Schirdewahn C; Eitel I; Adams V; Fuernau G; Erbs S; Linke A; Diederich KW; Nowak M; Desch S; Gutberlet M; Schuler G; Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial.; Journal of the American College of Cardiology; 2010; vol. 55 (no. 20)

Study details

Study location	Germany
Study setting	single centre cardiology department
Study dates	November 2006 - February 2008
Duration of follow-up	up to 6 months
Sources of funding	none reported
Inclusion criteria	Other patients with ST elevation MI undergoing primary angioplasty with moderate contrast volumes. MI symptoms for under 12 hours, ST segment elevation of at least 0.1mV in at least 2 extremity leads or at least 0.2mV in at least 2 precordial leads

Exclusion criteria	Allergy known NAC allergy or contraindication to MRI Medications known RRT Pregnancy or breastfeeding Procedures Previous fibrinolysis <12 hours
Sample size	249
Loss to follow-up	0
Interventions	Contrast type Low osmolar Contrast name iopromide Contrast procedure PCI
Outcome measures	Contrast induced AKI sCR ≥25% 72 hours after PCI Mortality at 6 months Adverse events during NAC administration Renal failure need for RRT

Study arms

	IV NAC + IV sodium chloride 0.9% (N = 126) Pre-contrast: 1200mg IV bd in single bolus Post-contrast: NAC given over 48 hours (4 doses) with 0.9% sodium chloride 1ml/kg/h given for 12 hours.

% Female	29.4%
Mean age (SD)	median 68 (IQR 57-75) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 81 (IQR 69-97) umol/L % Diabetes 25.4% % Hypertension 70.6% % ACEI 98.4% % NSAIDs 99.2%
Interventions	Contrast type Low osmolar Contrast name iopromide Contrast dose, ml, mean (SD) median 180 (IQR 140-230) ml Contrast procedure PCI

IV sodium chloride 0.9% (N = 123)

Pre-contrast: none Post-contrast: 0.9% sodium chloride 1ml/kg/h given for 12 hours.

% Female	34.4%
Mean age (SD)	median 68 (IQR 56 - 76) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 78 (IQR 67-90) umol/L % Diabetes 32.8% % Hypertension 73.6% % ACEI 97.6% % NSAIDs 99.2%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(although unclear if allocation)

Overall Directness

Directly applicable

Torigoe 2013

Bibliographic Reference	Torigoe, Kumie; Tamura, Akira; Watanabe, Toru; Kadota, Junichi; 20-Hour preprocedural hydration is not superior to 5-hour preprocedural hydration in the prevention of contrast-induced increases in serum creatinine and cystatin C; International journal of cardiology; 2013; vol. 167 (no. 5); 2200-3

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan

Study setting	Single hospital
Study dates	May 2010 - April 2011
Duration of follow-up	48 hours
Inclusion criteria	Age at least 20 years old eGFR 15-60ml/min/1.73m2 Other scheduled for elective coronary arteriography or PIC
Exclusion criteria	Other conditions ACS within the month preceding study; severe symptoms of heart failure, left ventricular EF <20%, severe hepatic insufficiency, severe chronic respiratory disease, singe function kidney, nephritic syndrome, multiple myeloma Allergy allergy to contrast medium Contrast IV contrast agent <5 days prior to study Medications administration of N-acetylcysteine, theophylline, dopamine, or mannitol History of dialysis Pregnancy or breastfeeding Procedures emergency coronary arteriography or PCI
Sample size	122
Interventions	Contrast type low-osmolar, non-ionic Contrast name iohexel Contrast procedure scheduled for elective coronary arteriography or PIC Intervention (more details) Saline given at 0.5ml/kg/hour in epoples with LVEF <40%, infusion was limited to 80 ml/hour in peoples weighing >80kg (40ml/hour if also have LVEF <40%. Diuretics were routinely withheld on day of procedure.
Outcome measures	Serum creatinine clearance at 48 hours, maximal absolute and % change in sCr

Study arms

IV sodium chloride 0.9% (5 hours) (N = 60)

Pre-procedure: given at a dose of 1ml/kg/hour for 5 hours Post-procedure: given at a dose of 1ml/kg/hour for 24 hours

% Female	21.7%
Mean age (SD)	75.8 (SD 7.8) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 112.3 (SD 34.5) umol/L % Diabetes 61.7% % Hypertension 93.3% % ACEI 30% Baseline eGFR, ml/min per 1.73m2, mean (SD) 43.7 (SD 11.5)
Interventions	Contrast type low-osmolar, non-ionic Contrast name iohexel Contrast dose, ml, mean (SD) 130.2 (53.8) ml Contrast procedure scheduled for elective coronary arteriography or PIC Intervention (more details) Saline given at 0.5ml/kg/hour in epoples with LVEF <40%, infusion was limited to 80 ml/hour in peoples weighing >80kg (40ml/hour if also have LVEF <40%. Diuretics were routinely withheld on day of procedure.

IV sodium chloride (20 hours) (N = 62)

Pre-procedure: given at a dose of 1ml/kg/hour for 20 hours Post-procedure: given at a dose of 1ml/kg/hour for 24 hours

	% Female	22.6%
	Mean age (SD)	74.5 (SD 9) years
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 114.9 (SD 39.8) umol/L % Diabetes 50% % Hypertension 93.5% % ACEI 40.3% Baseline eGFR, ml/min per 1.73m2, mean (SD) 43.9 (SD 12.1)
	Interventions	Contrast type low-osmolar, non-ionic Contrast name iohexel Contrast dose, ml, mean (SD) 122.9 (SD 53.7) ml Contrast procedure scheduled for elective coronary arteriography or PIC Intervention (more details) Saline given at 0.5ml/kg/hour in epoples with LVEF <40%, infusion was limited to 80 ml/hour in peoples weighing >80kg (40ml/hour if also have LVEF <40%. Diuretics were routinely withheld on day of procedure.

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear if allocation concealment; unblinded; unclear if missing data and approach to missing data)

Overall Directness

Directly applicable

Traub 2013

Bibliographic Reference	Traub, Stephen J.; Mitchell, Alice M.; Jones, Alan E.; Tang, Aimee; O'Connor, Jennifer; Nelson, Teresa; Kellum, John; Shapiro, Nathan I.; N-acetylcysteine plus intravenous fluids versus intravenous fluids alone to prevent contrast-induced nephropathy in emergency computed tomography; Annals of emergency medicine; 2013; vol. 62 (no. 5); 511-520.e25

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	EDs in 2 tertiary centres
Duration of follow-up	72 hours
Sources of funding	Sponsored through an investigator-initiated grant from Cumberland Pharmaceuticals.
Inclusion criteria	Age at least 18 years of age

	Other undergoing emergency enhanced CT of chest, abdomen, or pelvis as part of clinical care; 1 or more risk factors for contrast-induced nephropathy (pre-existing renal dysfunction, diabetes, hypertension being treated with antihypertensive medications, CAD, use of nephrotic drugs, liver disease, congestive heart failure, older age (65 years plus), and anemia.)
Exclusion criteria	Other conditions end-stage renal disease currently undergoing regular peritoneal or hemodialysis; or clinically unstable (30 min delay for infusion of study medication or placebo was contraindicated) Allergy known allergy to N-acetylcysteine Medications Pregnancy or breastfeeding Did not provide consent
Sample size	399
Loss to follow-up	42 missing outcome data
Interventions	Contrast name Isovue n=12 (6%) n=13 (7%) Optiray n=176 (91%) n=175 (91%) Visipaque n=5 (3%) n=5 (3%) Contrast procedure CT scan
Outcome measures	Contrast induced AKI at 48 to 72 hours, defined as an increase in sCr of at least 44.2 umol/L or 25% over baseline Renal failure moderate renal injury (100% increase in sCr level) or severe renal failure (necessitating RRT), telephone calls were used to identify those with renal injury beyond 72 hours

Study arms

	IV NAC + IV sodium chloride 0.9% (N = 203) Pre-procedure: 200 mg of NAC per hour administered as an infusion of 67 mL per hour of a solution of 3 g of NAC diluted to a total volume of 1,000 mL with 500 mL sodium chloride 0.9%. during 30 min. Post-procedure: IV sodium chloride 0.9% continuous infusion of 67 mL per hour for at least 2 hours.

% Female	62%
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 88.4 (SD 24.8) umol/L
Interventions	Contrast name Isovue n=12 (6%) Optiray n=176 (91%) Visipaque n=5 (3%) Contrast dose, ml, mean (SD) 113.11 (SD 22.95) Contrast procedure CT scan

IV sodium chloride 0.9% (N = 196)

Pre-procedure: 500 mL sodium chloride 0.9%. during 30 min. Post-procedure: IV sodium chloride 0.9% continuous infusion of 67 mL per hour for at least 2 hours.

% Female	57%
Mean age (SD)	59.7 (SD 15.9)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 87.5 (SD 23.9) umol/L
Interventions	Contrast name Isovue n=13 (7%) Optiray n=175 (91%) Visipaque n=5 (3%) Contrast dose, ml, mean (SD) 115.24 (SD 21.06) Contrast procedure CT scan

Risk of Bias

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear if allocation concealed; unclear how randomisation performed; trial terminated early and unclear stopping rules; unclear for reason for failure to follow up drop-outs)

Overall Directness

Directly applicable

Turedi 2016

Bibliographic Reference	Turedi, Suleyman; Erdem, Erkan; Karaca, Yunus; Tatli, Ozgur; Sahin, Aynur; Turkmen, Suha; Gunduz, Abdulkadir; The High Risk of Contrast-induced Nephropathy in Patients with Suspected Pulmonary Embolism Despite Three Different Prophylaxis: A Randomized Controlled Trial; Academic emergency medicine : official journal of the Society for Academic Emergency Medicine; 2016; vol. 23 (no. 10); 1136-1145

Study details

Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Emergency department of a tertiary care university hospital receiving > 100,000 patient presentations annually.
Study dates	February 1, 2014 - February 1, 2015

Duration of follow-up	Post-CTPA infusion was maintained for at least 6 hours.
Inclusion criteria	Age at least 18 years old Other Undergoing contrast enhanced thoracic CT due to suspected PE, with measurable basal creatinine levels pretomography, measurable serum creatinine levels 48-72 hours posttomography CIN One or more risk factors for CIN
Exclusion criteria	Other conditions patients requiring NAC therapy or NaHCO3 therapy for existing additional disease Allergy known allergy to NAC or NaHCO3 Contrast exposed to contrast material for any reason in the previous 10 days or during the in-hospital follow-up period and patients who refused to participate were excluded Medications "if the physician responsible for treatment in the emergency department considered that the study protocol would be liable to delay medical care or have adverse effects, or if any of the drugs in the protocol were thought to be contraindicated, such patients were also excluded." History of dialysis disease already in dialysis or hemodialysis Pregnancy or breastfeeding
Sample size	231
Loss to follow-up	26
Interventions	Contrast type non-ionic, low-osmolar contrast agent Contrast name Unclear Contrast dose, ml, mean (SD) all patients received less than 100 ml Contrast procedure CTPA
Outcome measures	Renal failure moderate renal injury (defined as a 100% increase in serum creatinine levels) or severe renal failure developing (requiring hemodialysis or peritoneal dialysis)

	CIN CIN development measurement of the changes in pre- CTPA basal creatinine levels and post-CTPA creatinine levels measured 48–72 hours following contrast exposure and an increase ≥25% or 0.5 mg/dL in creatinine levels 48–72 hours after contrast exposure compared to basal levels

Study arms

IV NAC + IV sodium chloride 0.9% (N = 85)

Pre-CTPA: 3 mL/kg IV NAC+NS solution (3 g NAC was made up to 1000 mL with NS) Post-CTPA: 1 mL/kg

% Female	51.8%
Mean age (SD)	median 76.0 (95%CIs 72.0-80.0) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 9.4% > 132 umol/L % CKD 10.6% % Diabetes 12.9% % Hypertension 43.5% % ACEI 12.9% % NSAIDs 3.5% Baseline eGFR, ml/min per 1.73m2, mean (SD) 88.9 (73.9–104.0)

IV sodium chloride 0.9% + IV sodium bicarbonate (N = 85)

Pre-CTPA: 3 mL/kg 132 mEq NaHCO3 was made up to 1000 mL with NS Post-CTPA: 1ml/kg for a minimum of 6h

% Female	49.4%
Mean age (SD)	Median 77.0 (9

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 11.8% > 132 umol/L % CKD 7.1% % Diabetes 16.5% % Hypertension 44.7% % ACEI 16.5% % NSAIDs 5.9% Baseline eGFR, ml/min per 1.73m2, mean (SD) basal* 85.0 (95% CIs 71.5-98.5)

IV sodium chloride 0.9% (N = 87)

Pre-CTPA: 3 mL/kg NS alone for 1 hour Post-CTPA: 1 mL/kg IV per hour for a minimum of 6 hour

% Female	47.1%
Mean age (SD)	Median 74.0 (73.0 - 75.9)
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 12.6% >132 umol/L % CKD 11.5% % Diabetes 13.8% % Hypertension 49.4% % ACEI 20.7% % NSAIDs 3.4% Baseline eGFR, ml/min per 1.73m2, mean (SD) Basal* 85.0 (95%CIs 71.5-98.5)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(although unclear if allocation concealment)

Overall Directness

Directly applicable

Ueda 2011

Bibliographic Reference	Ueda, Hiromichi; Yamada, Takahisa; Masuda, Masaharu; Okuyama, Yuji; Morita, Takashi; Furukawa, Yoshio; Koji, Tanaka; Iwasaki, Yusuke; Okada, Takeshi; Kawasaki, Masato; Kuramoto, Yuki; Naito, Takashi; Fujimoto, Tadao; Komuro, Issei; Fukunami, Masatake; Prevention of Contrast-Induced Nephropathy by Bolus Injection of Sodium Bicarbonate in Patients With Chronic Kidney Disease Undergoing Emergent Coronary Procedures; The American Journal of Cardiology; 2011; vol. 107 (no. 8); 1163-1167

Study details

Study type	Randomised controlled trial (RCT)

Study location	Japan
Study setting	Single centre
Study dates	June 2008 - February 2010
Duration of follow-up	72 hours
Sources of funding	none reported
Inclusion criteria	Age >20 years Other undergoing emergency diagnostic or interventional coronary procedure (such as coronary angiography or PCI), the incidations was suspected acute coronary syndrome. Chronic kidney disease renal insufficiency (sCr >97.2 umol/L or eGFR <60 ml/min.
Exclusion criteria	Allergy allergy to contrast media Contrast exposure to contrast media within 2 days before study. Medications previous or planned mannitol, fenoldopam, N-acetylcysteine, theophylline, dopamine, or non-study sodium bicarbonate. History of dialysis Pregnancy or breastfeeding Serum creatinine change in sCr of at least 44.2 umol/L during the 24 hours before the procedure
Sample size	60
Loss to follow-up	1
Interventions	Contrast type nonionic, low-osmolality Contrast name Iohexel or iopamidol Contrast procedure

	emergency diagnostic or interventional coronary procedure (such as coronary angiography or PCI)
Outcome measures	Contrast induced AKI at 48 hours, defined as an increase of at least 44.2 umol/L or 25% over baseline sCr.

Study arms

IV sodium chloride 0.9% + IV sodium bicarbonate (N = 30)

Pre-procedure: IV sodium chloride 0.9% 0.5 ml/kg as soon as possible after they were admitted, before the administration of contrast. Post-procedure: 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure.

% Female	21%
Mean age (SD)	75 (SD 10) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 133.5 (SD 52.2) umol/L % Diabetes 20% % ACEI 62%
Interventions	Contrast type nonionic, low-osmolality Contrast name Iohexel or iopamidol Contrast dose, ml, mean (SD) 104 (SD 57) umol/L Contrast procedure emergency diagnostic or interventional coronary procedure (such as coronary angiography or PCI)

IV sodium bicarbonate (N = 30)

Pre-procedure: none Post-procedure: 154 mEq/L sodium bicarbonate at 1 ml/kg/hour during and for 6 hours after the coronary procedure.

% Female	23%

	Mean age (SD)	77 (SD 9) years
	Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 116.7 (40.7) umol/L % Diabetes 10% % ACEI 80%
	Interventions	Contrast type nonionic, low-osmolality Contrast name Iohexel or iopamidol Contrast dose, ml, mean (SD) 116 (SD 63) umol/L Contrast procedure emergency diagnostic or interventional coronary procedure (such as coronary angiography or PCI)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Trial terminated early with no apparent pre-planned interim analysis or stopping rules outlined; unclear if allocation concealment)

Overall Directness

Directly applicable

Van Mourik 2018

Bibliographic Reference	van Mourik, M. S.; van Kesteren, F.; Planken, R. N.; Stoker, J.; Wiegerinck, E. M. A.; Piek, J. J.; Tijssen, J. G.; Koopman, M. G.; Henriques, J. P. S.; Baan, J., Jr.; Vis, M. M.; Short versus conventional hydration for prevention of kidney injury during pre-TAVI computed tomography angiography; Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation; 2018; vol. 26 (no. 9); 425-432

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	3 centres
Study dates	January 2015 - August 2016
Duration of follow-up	5 days
Sources of funding	none reported
Inclusion criteria	Age >18 years Other planned for CTA prior to TAVI Chronic kidney disease 3a or above
Exclusion criteria	Other conditions multiple myeloma, Waldenstrom's disease and LVEF <20%

	Allergy known iodine allergy Contrast contrast administration <7 days History of dialysis already on haemodialysis
Sample size	84 (74 analysed)
Loss to follow-up	10
Interventions	Contrast type non-ionic low-osmolar Contrast name Iopromide Contrast dose, ml, mean (SD) 90 ml iopromide 300mg I/ml Contrast procedure CTA
Outcome measures	Contrast induced AKI at 2-5 days, defined as increase in creatinine of at least 25% or 44.2umol/L over baseline Notes mean change in eGFR and hydration volumes, increase in self-reported dyspnoea according to Borg scale, acute heart failure, absolute change in N-terminal pro-hormone of brain natriuretic peptide with 2-5 days, all also recorded Serum creatinine clearance % change in sCr between the two hydration protocols at 2-5 days after contrast administration, compared to baesline; absolute change in creatinine.

Study arms

	Sodium bicarbonate (N = 39) pre-procedure: 1.4% 3ml/kg/h given for 1 hour post-procedure: none
% Female	48.7
Mean age (SD)	median 81.2 (IQR 77.7-84.9) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 109 (IQR 94-135) umol/L % Diabetes 35.9% % Hypertension 82% Baseline eGFR, ml/min per 1.73m2, mean (SD) median 46 (IQR 35-52)

Sodium chloride 0.9% (N = 35)

pre-procedure: 1ml/kg/h for 8 hours post-procedure: 1ml/kg/h for 16 hours

% Female	62.9%
Mean age (SD)	median 83 (IQR 80.7-86.4) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 99 (IQR 88-119) umol/L % Diabetes 25.7% % Hypertension 74.3% Baseline eGFR, ml/min per 1.73m2, mean (SD) median 49 (IQR 40-53)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Vasheghani-Farahani 2010

Bibliographic Reference	Vasheghani-Farahani A; Sadigh G; Kassaian SE; Khatami SM; Fotouhi A; Razavi SA; Mansournia MA; Kazemisaeid A; Soleimani A; Pourhosseini HR; Alidoosti M; Hajizeinali AM; Hoseini K; Nematipour E; Sodium bicarbonate in preventing contrast nephropathy in patients at risk for volume overload: a randomized controlled trial.; Journal of nephrology; 2010; vol. 23 (no. 2); 216-223

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Single centre
Study dates	August 2007 - July 2008
Duration of follow-up	up to 5 days
Sources of funding	Supported by Tehran University
Inclusion criteria	Serum creatinine Age at least 18 years old Other

	candidate for coronary angiography and having at least one of the following: uncontrolled hypertension, compensated severe heart failure (EF <30% or grades III-IV) or a previous pulmonary edema.
Exclusion criteria	Other conditions need for continuous hydration (e.g. sepsis); or multiple myeloma Contrast allergy to contrast agent Medications dopamine, mannitol fenoldopam or N-acetylcysteine during intended time of study History of dialysis Pregnancy or breastfeeding Procedures emergency catheterization; recent exposure to radiographic contrast agents (<2 days prior to study) Serum creatinine unstable sCr (changes in >44.2 umol/L or 25% from creatinine measures prior to the study to that of the day of angiography) eGFR <20ml/min per 1.73m2
Sample size	72
Interventions	Contrast type low osmolar Contrast name Iohexel (omnipaque) Contrast dose, ml, mean (SD) 350mg I/mL Contrast procedure angiography
Outcome measures	Contrast induced AKI at 48 hours and at 5 days, defined as an increase in absolute (at least 44.2 umol/L) or relative (at least 25%) increase over baseline. Length of hospital stay Notes urine pH was also assessed after initial bolus

Study arms

	IV sodium bicarbonate _ sodium chloride 0.45% (N = 36)

Pre-procedure: 75 mL of 8.4% sodium bicarbonate to 1 L sodium chloride 0.45% given at 3 ml/kg for 1 hour. Post-procedure: same again, given at 1ml/kg for 6 hours.

Study setting	Single centre
% Female	22.2%
Mean age (SD)	61.4 (SD 9) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 156.5 (SD 46.0) umol/L % Diabetes 33.3% % Hypertension 65.7% % ACEI 52.9%

Sodium chloride 0.45% (N = 36)

Pre-procedure: 1075 mL sodium chloride 0.45% given at 3 ml/kg for 1 hour. Post-procedure: same again, given at 1ml/kg for 6 hours.

Study setting	SIngle centre
% Female	19.4%
Mean age (SD)	62.7 (SD 11) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 151.2 (SD 39.8) umol/L % Diabetes 38.2% % Hypertension 70.6% % ACEI 47.1%

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

Some concerns

(Unclear if allocation concealment; study terminated early with no pre-defined stopping rules)

Overall Directness

Directly applicable

Webb 2004

Bibliographic Reference	Webb JG; Pate GE; Humphries KH; Buller CE; Shalansky S; Al Shamari A; Sutander A; Williams T; Fox RS; Levin A; A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect.; American heart journal; 2004; vol. 148 (no. 3)

Study details

Study location	Canada
Study setting	in/outpatient tertiary care cardiac unit

Study dates	unclear
Duration of follow-up	in-hospital and call at 2 days post procedure
Sources of funding	Tyco Canada (suppliers of ioversol), Shiley Canada Inc, Vancouver Hospital Interventional Trust.
Inclusion criteria	Age at least 18 years old eGFR Screening GFR <50ml/min Other Patients with renal dysfunction undergoing cardiac catheterisation or PCI
Exclusion criteria	Other conditions acute renal failure or unstable clinical status Medications NAC administration within 48 hours or concurrent RRT Serum creatinine creatinine >400umol/L or recent creatinine elevation after diagnostic angiogram Unable to comply with follow-up
Sample size	398
Loss to follow-up	89 (78;did not have adequate creatinine measurement, 10 excluded and 1 did not receive study drug)
Interventions	Contrast type Low osmolar Contrast name Ioversol Contrast dose, ml, mean (SD) median 120 (IQR 80-175) Contrast procedure PCI
Outcome measures	Contrast induced AKI at 72 hours, defined as reduction in CrCl from baseline of >5ml/min day 2-8, median day 3) Mortality in-hospital mortality Renal failure need for RRT

	Serum creatinine clearance at 72 hours: increase in serum creatinine of at least 25% or at least 44 umol/L day 2-8 (median day 3)

Study arms

IV NAC + IV sodium chloride 0.9% (N = 194)

Pre-contrast: 200ml 0.9% sodium chloride, plus 500mg (in 50ml of 5% dextrose saline) given over 15 mins within 1 hours of procedure. Post-contrast: 0.9% 1.5ml/kg/hour sodium chloride for 6 hours.

% Female	40.5%
Mean age (SD)	70.8 (SD 10.3) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 141 (IQR 125 - 166) % Diabetes 30.6% % ACEI 68.1% ARB or ACEI

IV sodium chloride 0.9% (N = 204)

Pre-contrast: 200ml 0.9% sodium chloride, plus 50ml of 5% dextrose saline (without NAC) given over 15 mins within 1 hours of procedure. Post-contrast: 0.9% 1.5ml/kg/hour sodium chloride for 6 hours.

% Female	38.0%
Mean age (SD)	70.0 (SD 9.4) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) median 142 (IQR 124 - 167) % Diabetes 39.2% % ACEI 70.0% ACEI or ARB

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

High

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(Follow up was incomplete in >5% but unclear proportion of missing outcome data between arms; Unclear how randomisation performed; unclear reasons for missing creatinine on follow up; follow up creatinine was recorded for each participant on one occasion between day 2 - 8 post-procedure; unclear how length of time to follow up varied between study arms)

Overall Directness

Directly applicable

Weisbord 2018

Bibliographic Reference	Weisbord, Steven D.; Gallagher, Martin; Jneid, Hani; Garcia, Santiago; Cass, Alan; Thwin, Soe-Soe; Conner, Todd A.; Chertow, Glenn M.; Bhatt, Deepak L.; Shunk, Kendrick; Parikh, Chirag R.; McFalls, Edward O.; Brophy, Mary; Ferguson, Ryan; Wu, Hongsheng; Androsenko, Maria; Myles, John; Kaufman, James; Palevsky, Paul M.; Group, Preserve Trial; Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine; The New England journal of medicine; 2018; vol. 378 (no. 7); 603-614

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Multisite: Veterans Affairs sites and George Institute sites
Study dates	February 2013 through March 2017
Duration of follow-up	90 to 104 days
Sources of funding	U.S. Department of Veterans Affairs Cooperative Studies Program and the George Institute for Global Health.
Inclusion criteria	eGFR 15 to 44.9 ml per minute per 1.73 m² of body-surface area or 45 to 59.9 ml per minute per 1.73 m² among those with diabetes mellitus received imaging Patients who were scheduled to undergo coronary or noncoronary angiography Other able and willing to provide informed consent
Exclusion criteria	Other conditions Decompensated heart failure Allergy known allergy to NAC or anaphylactive allergy to iodinated contrast Contrast receipt of iodinated contrast in past 5 days Age <18 years old History of dialysis receiving dialysis Pregnancy or breastfeeding Pregnancy Related conditions Stage 5 CKD Procedures Undergoing emergency angiography Serum creatinine unstable baseline levels of blood creatinine (which was defined as an increase or decrease of ≥25% within 3 days before angiography) Unable to comply with follow-up

	for 4 or 90 day outcome assessment other Prisoner; ongoing participation in unapproved concurrent interventional trial
Sample size	5177
Loss to follow-up	184 excluded after randomisation
Interventions	Contrast type nonionic, low osmolar and iso-osmolar contrasts Contrast name Iodixanol, Iopamidol, Iohexol, and "other low osmolal agents" Contrast procedure Angiography: coronary, peripheral, carotid, mesenteric, aortic, renal, and other
Outcome measures	CKD progression confirmed persistent kidney impairment at 90 to 104 days Mortality within 90 days Adverse events hospitalization with acute coronary syndrome, heart failure, or stroke within 90 days. Hospitalization for any cause within 90 days Need for dialysis within 90 days CIN an increase in serum creatinine of either at least 25% or at least 0.5 mg per deciliter (44 µmol per liter) from baseline at 3 to 5 days after angiography Composite outcome death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 to 104 days after angiography and confirmed at subsequent testing within 14 days (defined as persistent impairment in kidney function).

Study arms

	oral NAC + IV sodium chloride 0.9% (N = 1238) oral NAC dose: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days (total oral NAC 2400mg daily for 5 days) IV sodium chloride 0.9% dose: 154 mmol per liter. 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 to 12 ml/kg after angiography.

% Female	6.1
Mean age (SD)	69.8 (8.3)
Condition specific characteristics	% Diabetes 81.5 % Hypertension 94.6 Baseline serum creatinine, mg/dl, median (IQR) 1.5 (1.3 - 1.78)
Interventions	Contrast type nonionic, low osmolar and iso-osmolar contrasts Contrast name Iodixanol (56.2%), Iopamidol (24.1%), Iohexol (10.9%), and "other low osmolal agents" (8.8%) Contrast procedure Angiography: coronary (91.8%), peripheral (6.5%), carotid (0.3%), mesenteric (0.1%), aortic (0.4%), renal (0.3%), and other (0.6%) Contrast dose, ml, median (IQR) 85 (55 - 140)

placebo + IV sodium chloride 0.9% (N = 1244)

oral placebo dose: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days. IV sodium chloride 0.9% dose: 154 mmol per liter. 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 to 12 ml/kg after angiography.

% Female	7
Mean age (SD)	69.6 (8.4)
Condition specific characteristics	% Diabetes 81.6 % Hypertension 94.6 Baseline serum creatinine, mg/dl, mean (SD) 50.7 (41.1 - 59.8)
Interventions	Contrast type

	nonionic, low osmolar and iso-osmolar contrasts Contrast name Iodixanol (56.8%), Iopamidol (23.1%), Iohexol (11.3%), and "other low osmolal agents" (8.8%) Contrast procedure Angiography: coronary (89.6%), peripheral (7.7%), carotid (0.7%), mesenteric (0.1%), aortic (0.7%), renal (0.5%), and other (0.7%) Contrast dose, ml, median (IQR) 85 (55 - 135)

oral NAC + IV sodium bicarbonate (N = 1257)

oral NAC: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days (total oral NAC 2400mg daily for 5 days) IV sodium bicarbonate dose: 1.26% (150 mmol per liter). 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 - 12 ml/kg after angiography.

% Female	5.8
Mean age (SD)	70.2 (8.0)
Condition specific characteristics	% Diabetes 79.9 % Hypertension 94.0 Baseline serum creatinine, mg/dl, median (IQR) 1.5 (1.3 - 1.7)
Interventions	Contrast type nonionic, low osmolar and iso-osmolar contrasts Contrast name Iodixanol (57.7), Iopamidol (23.4), Iohexol (10.9%), and "other low osmolal agents" (8.1%) Contrast procedure Angiography: coronary (89.5%), peripheral (7.5%), carotid (0.9%), mesenteric (0.1%), aortic (1.1%), renal (0.5%), and other (0.5%) Contrast dose, ml, median (IQR) 85 (55 - 138)

placebo + IV sodium bicarbonate (N = 1254)

	oral placebo: 1200 mg. 1 hour before and after contrast, and twice daily for the following 4 days. IV sodium bicarbonate dose: 1.26% (150 mmol per liter). 1-3 ml/kg/h during 1 - 12 hours for a total volume of 3 - 12 ml/kg pre-contrast. 1 - 1.5 ml/kg per hour during angiography. 1 - 3 ml/kg/h over 2 to 12 h for a total volume of 6 - 12 ml/kg after angiography.

% Female	6.9
Mean age (SD)	69.6 (8.3)
Condition specific characteristics	% Diabetes 81.0 % Hypertension 94.7 Baseline serum creatinine, mg/dl, median (IQR) 1.5 (1.3 - 1.8)
Interventions	Contrast type nonionic, low osmolar and iso-osmolar contrasts Contrast name Iodixanol (55.6%), Iopamidol (23.9%), Iohexol (11.8%), and "other low osmolal agents" (8.7%) Contrast procedure Angiography: coronary (91.0%), peripheral (6.6%), carotid (0.6%), mesenteric (0.1%), aortic (0.3%), renal (0.9%), and other (0.5%) Contrast dose, ml, median (IQR) 85 (58 - 135)

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

(Trial terminated early but with planned interim analysis and pre-defined stopping rules)

Overall Directness

Directly applicable

Wrobel 2010

Bibliographic Reference	Wrobel, Wojciech; Sinkiewicz, Wladyslaw; Gordon, Marcin; Wozniak-Wisniewska, Anita; Oral versus intravenous hydration and renal function in diabetic patients undergoing percutaneous coronary interventions; Kardiologia polska; 2010; vol. 68 (no. 9); 1015-20

Study details

Study type	Randomised controlled trial (RCT)
Study location	Poland
Study setting	single centre, cardiology department
Duration of follow-up	72 hours
Sources of funding	none reported
Inclusion criteria	Diabetes mellitus undergoing coronary angiography and/or angioplasty Other cardiovascular disease
Exclusion criteria	Other conditions

	Symptoms and signs of infection; co-morbid cancer; acute renal failure of alternative aetiology; participation in other studies in preceding 30 days Allergy History of hypersensitivity to contrast agents Medications antiobiotic treatment Pregnancy or breastfeeding Procedures Contraindication for invasive procedure
Sample size	102
Loss to follow-up	0
% Female	43.1%
Interventions	Contrast type low-osmolar Contrast name ioversol Contrast procedure angiography and/or angioplasty
Outcome measures	Contrast induced AKI at 48 and 72 hours: defined as an increase in serum creatinine of at least 25% or 44umol/L over baseline Renal failure need for RRT

Study arms

	Sodium chloride 0.9% (N = 52) Pre contrast: 6 hours Post-contrast: 12 hours both given at a dose of 1ml/kg/h intravenously

% Female	only reported overall
Mean age (SD)	67.3 (SD7.76) years

Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 109.2 (SD 39.4) umol/L % Diabetes 100%
Interventions	Contrast type low-osmolar Contrast name ioversol Contrast dose, ml, mean (SD) 101 (SD 36.7) ml Contrast procedure angiography and/or angioplasty

Oral mineral water or boiled water (N = 50)

Pre contrast: 6-12 hours Post-contrast: 12 hours both given at a dose of 1ml/kg/h

% Female	only reported overall
Mean age (SD)	63.7 (SD 7.82) years
Condition specific characteristics	Baseline serum creatinine, µmol/l, mean (SD) 103.6 (SD 34.2) umol/L % Diabetes 100%
Interventions	Contrast type low-osmolar Contrast name ioversol Contrast dose, ml, mean (SD) 110.4 (SD 45.2) ml Contrast procedure angiography and/or angioplasty

Risk of Bias Assessment

Domain 1: Bias arising from the randomisation process **Risk of bias judgement for the randomisation process**

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

Overall bias and Directness

Risk of bias judgement

High

(Unclear how randomisation was performed or if allocation concealment; unclear analytical approach to missing data or exclusions post-randomisation; unclear if exclusions or missing outcome data; non-blinded; unclear if trial analysed in accordance with finalised and pre-specified plan)

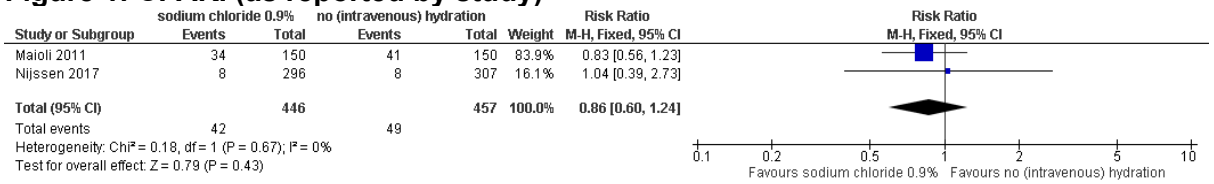
Overall Directness

Directly applicable

Appendix F – Forest plots of pairwise meta-analysis

Sodium chloride 0.9% vs no (intravenous) hydration

Figure 1: CI-AKI (as reported by study)



Sodium chloride 0.9% vs oral fluids

Figure 2: CI-AKI (as reported by study)

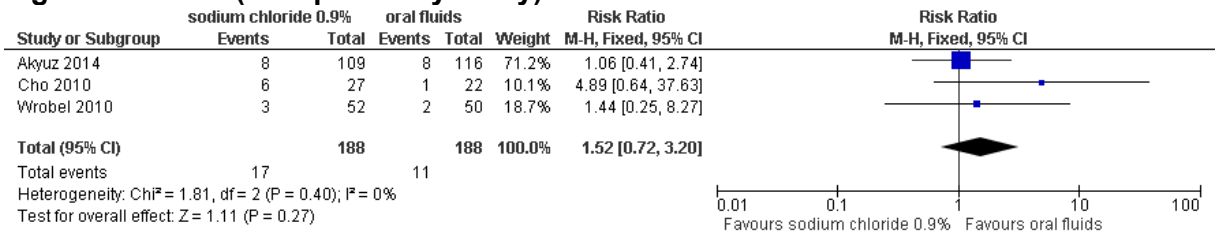
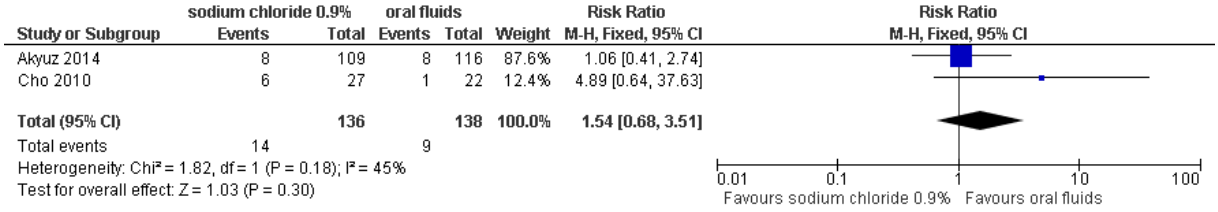


Figure 3: Sensitivity analysis excluding studies with a high risk of bias: Sodium chloride 0.9% vs oral fluids for CI-AKI (as reported by study)



Sodium chloride 0.9% vs sodium bicarbonate

Figure 4: CI-AKI (as reported by study)

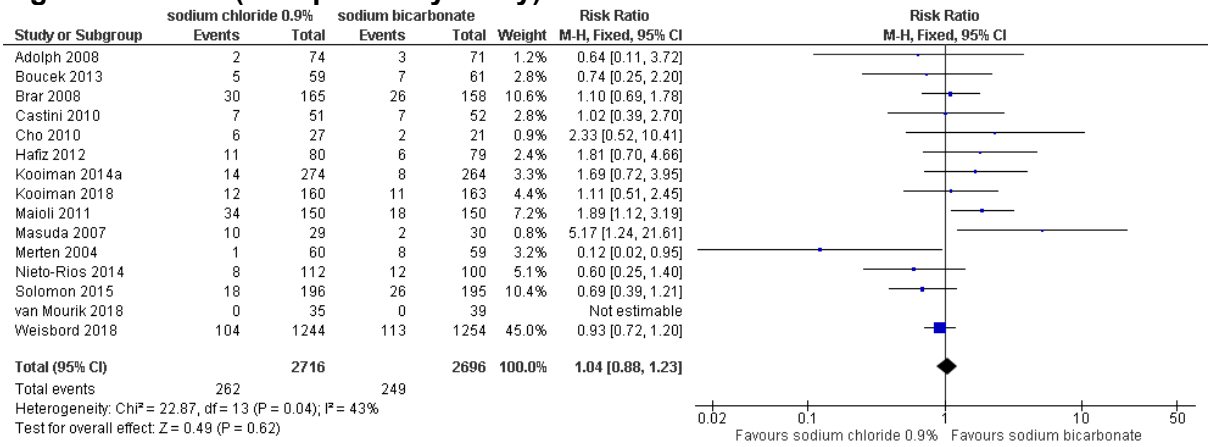


Figure 5: Funnel plot for sodium chloride 0.9% vs sodium bicarbonate for CI-AKI (as reported by study)

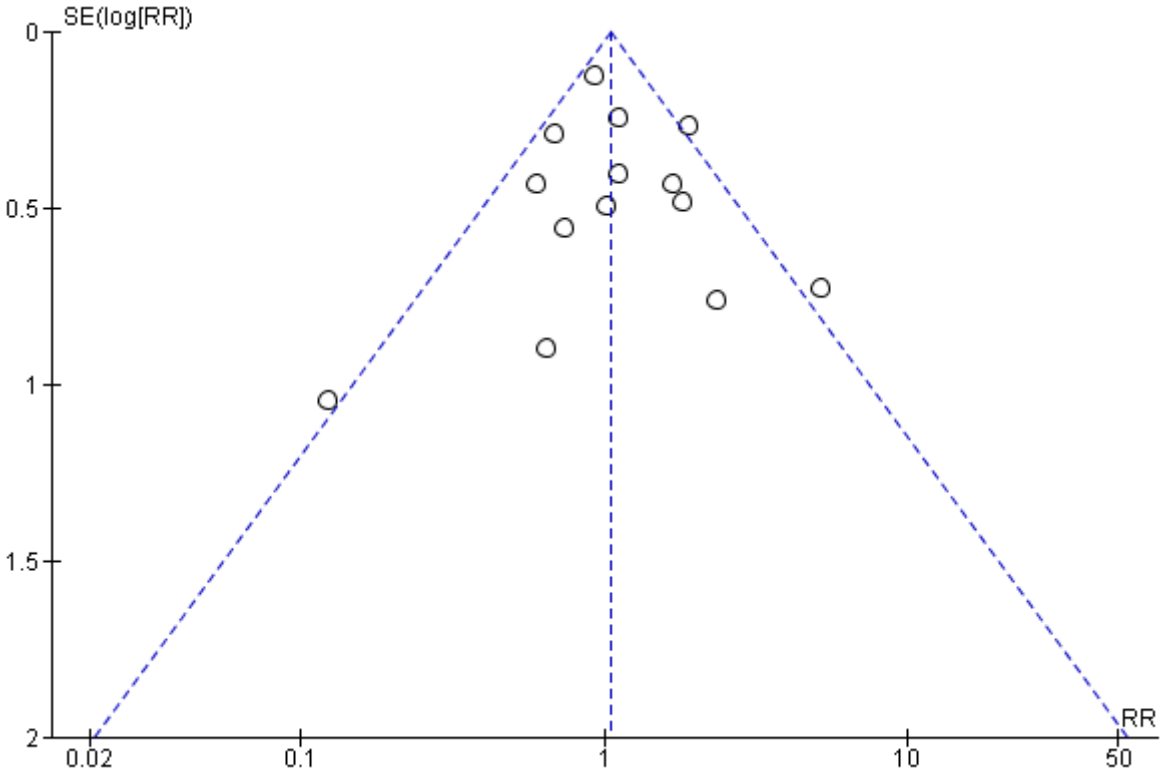
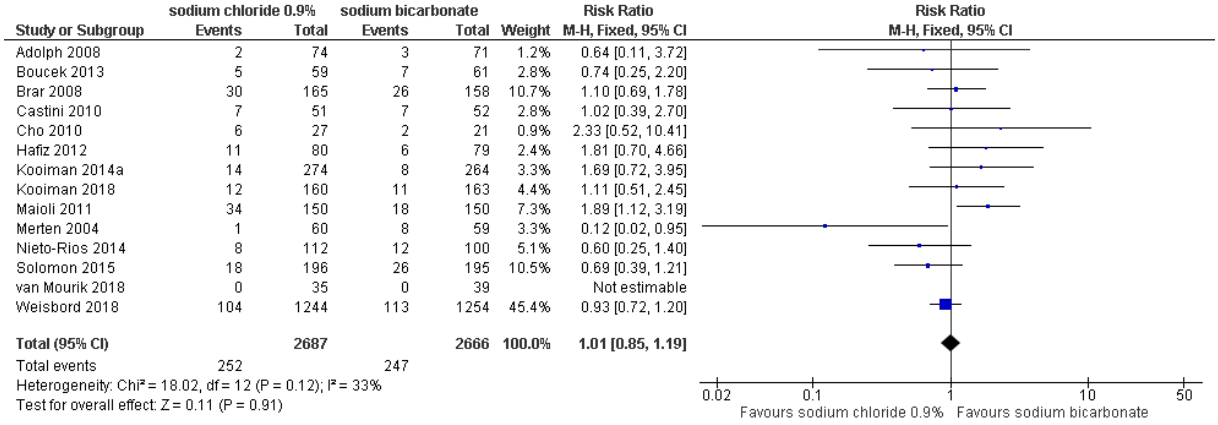
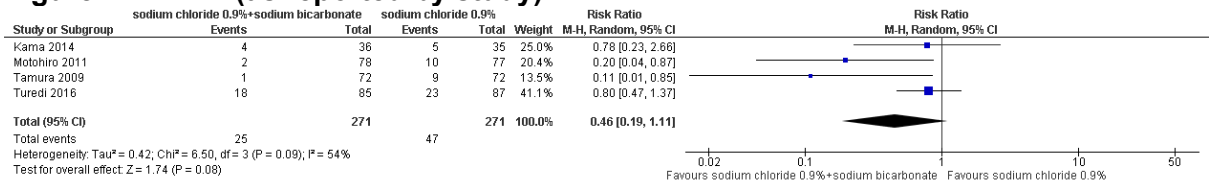


Figure 6: Sensitivity analysis excluding studies with a high risk of bias: Sodium chloride 0.9% vs sodium bicarbonate for CI-AKI (as reported by study)



Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9%

Figure 7: CI-AKI (as reported by study)



Sodium bicarbonate vs no (intravenous) hydration

Figure 8: CI-AKI (as reported by study)

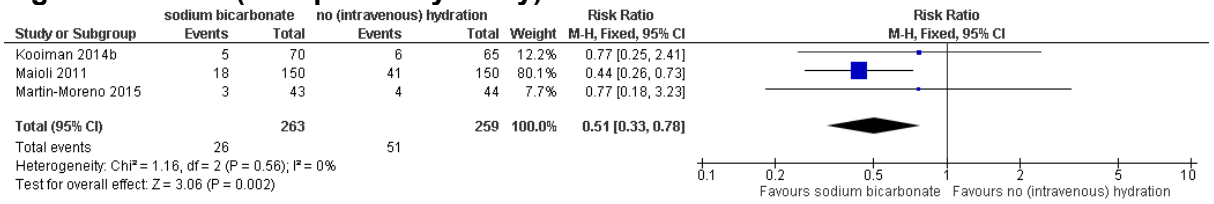
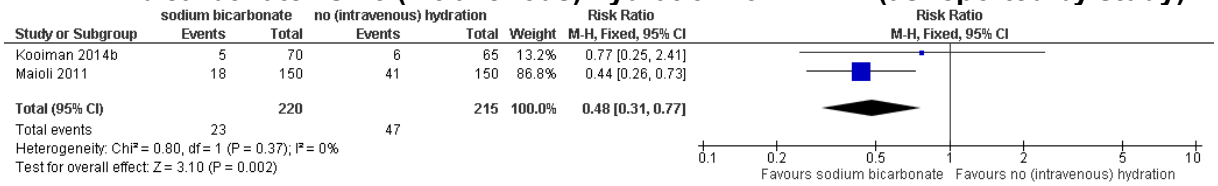
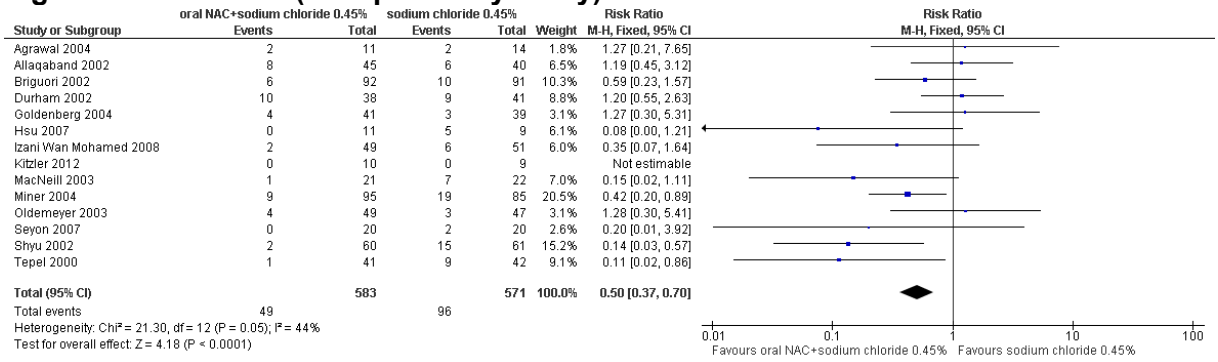


Figure 9: Sensitivity analysis excluding studies with a high risk of bias: Sodium bicarbonate vs no (intravenous) hydration for CI-AKI (as reported by study)



Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Figure 10: CI-AKI (as reported by study)



Study or Subgroup	oral NAC+sodium chloride 0.45% Events	Total	sodium chloride 0.45% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agrawal 2004	2	11	2	14	1.8%	1.27 [0.21, 7.65]
Allaqaband 2002	8	45	6	40	6.5%	1.19 [0.45, 3.12]
Briguori 2002	6	92	10	91	10.3%	0.59 [0.23, 1.57]
Durham 2002	10	38	9	41	8.8%	1.20 [0.55, 2.63]
Goldenberg 2004	4	41	3	39	3.1%	1.27 [0.30, 5.31]
Hsu 2007	0	11	5	9	6.1%	0.08 [0.00, 1.21]
Izani Wan Mohamed 2008	2	49	6	51	6.0%	0.35 [0.07, 1.64]
Kitzler 2012	0	10	0	9		Not estimable
MacNeill 2003	1	21	7	22	7.0%	0.15 [0.02, 1.11]
Miner 2004	9	95	19	85	20.5%	0.42 [0.20, 0.89]
Oldemeyer 2003	4	49	3	47	3.1%	1.28 [0.30, 5.41]
Seyon 2007	0	20	2	20	2.6%	0.20 [0.01, 3.92]
Shyu 2002	2	60	15	61	15.2%	0.14 [0.03, 0.57]
Tepel 2000	1	41	9	42	9.1%	0.11 [0.02, 0.86]
Total (95% CI)		**583**		**571**	**100.0%**	**0.50 [0.37, 0.70]**
Total events	49		96			

Heterogeneity: Chi² = 21.30, df = 12 (P = 0.05); I² = 44%
Test for overall effect: Z = 4.18 (P < 0.0001)

Figure 11: Funnel plot for oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% for CI-AKI (as reported by study)

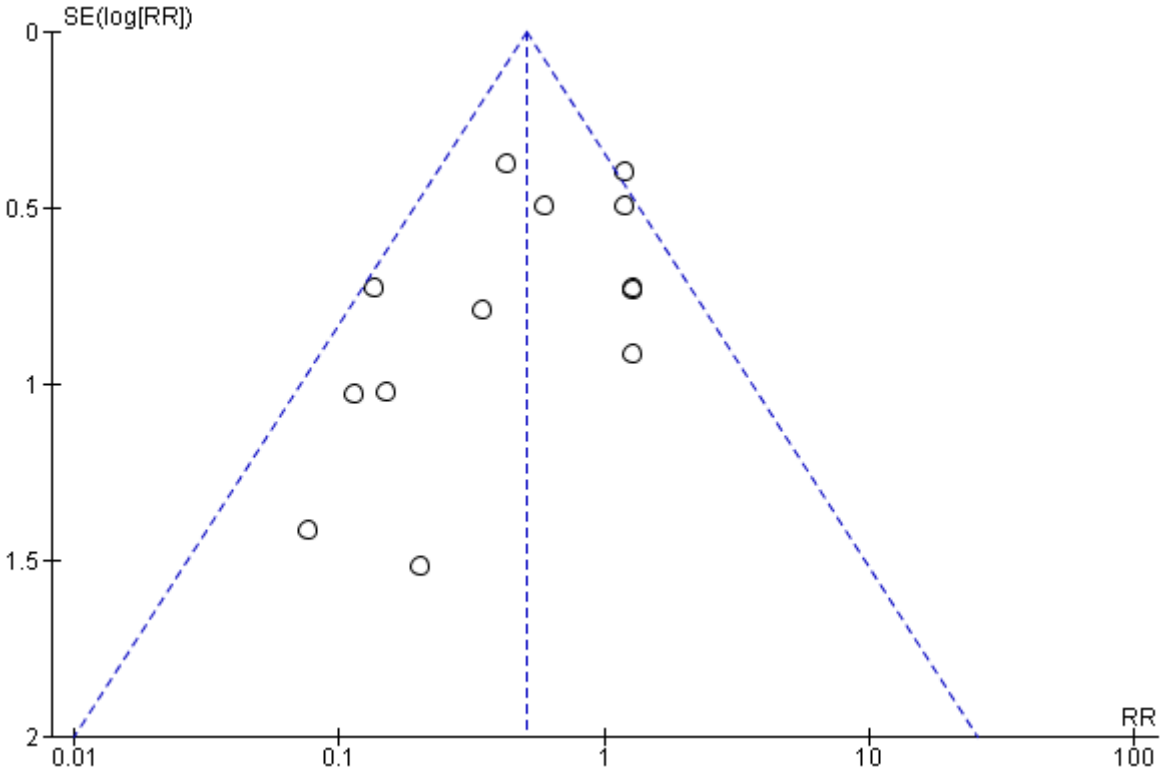
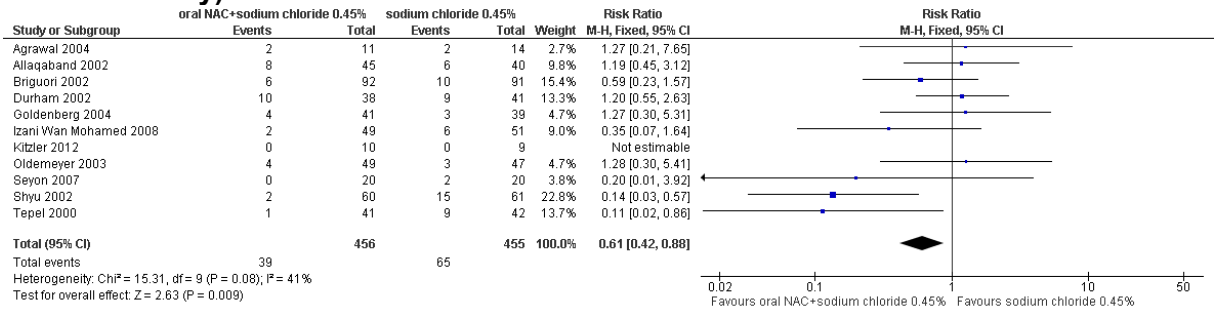


Figure 12: Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%for CI-AKI (as reported by study)



Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Figure 15: CI-AKI (as reported by study)

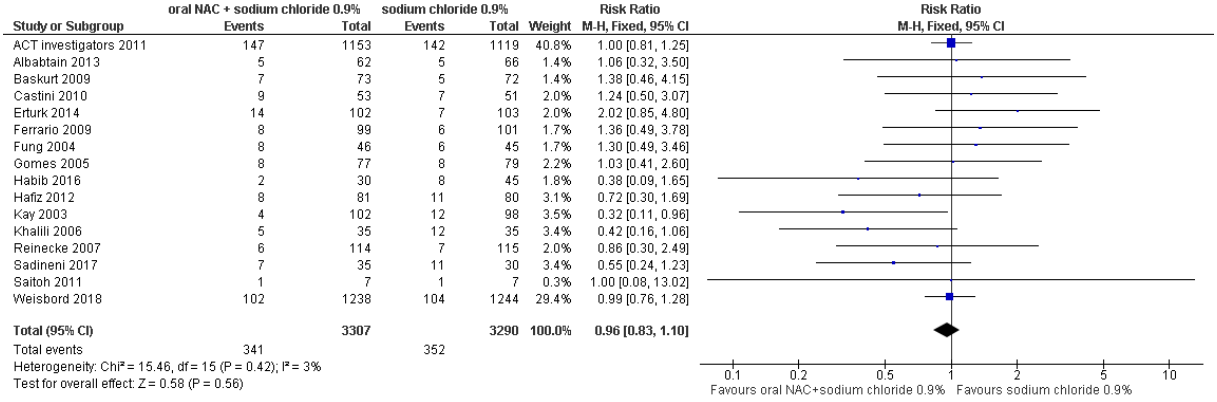


Figure 16: Funnel plot for oral NAC + sodium chloride 0.9% vs sodium chloride 0.9% for CI-AKI (as reported by study)

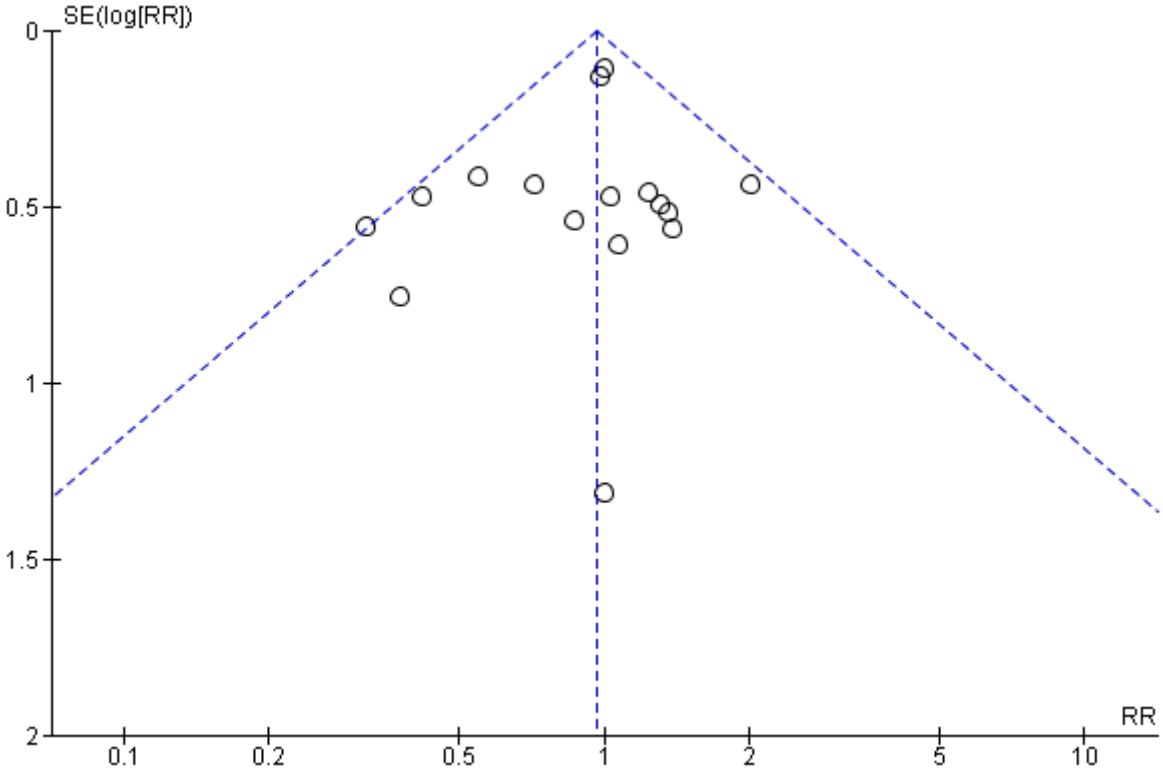
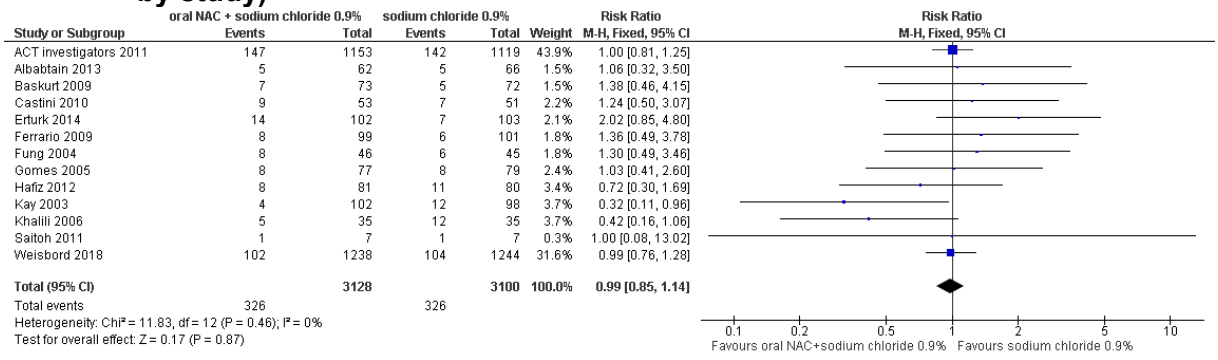


Figure 17: Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45% for CI-AKI (as reported by study)



Study or Subgroup	oral NAC + sodium chloride 0.9% Events	Total	sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACT investigators 2011	147	1153	142	1119	43.9%	1.00 [0.81, 1.25]
Albabtain 2013	5	62	5	66	1.5%	1.06 [0.32, 3.50]
Baskurt 2009	7	73	5	72	1.5%	1.38 [0.46, 4.15]
Castini 2010	9	53	7	51	2.2%	1.24 [0.50, 3.07]
Erturk 2014	14	102	7	103	2.1%	2.02 [0.85, 4.80]
Ferrario 2009	8	99	6	101	1.8%	1.36 [0.49, 3.78]
Fung 2004	8	46	6	45	1.8%	1.30 [0.49, 3.46]
Gomes 2005	8	77	8	79	2.4%	1.03 [0.41, 2.60]
Hafiz 2012	8	81	11	80	3.4%	0.72 [0.30, 1.69]
Kay 2003	4	102	12	98	3.7%	0.32 [0.11, 0.96]
Khalili 2006	5	35	12	35	3.7%	0.42 [0.16, 1.06]
Saitoh 2011	1	7	1	7	0.3%	1.00 [0.08, 13.02]
Weisbord 2018	102	1238	104	1244	31.6%	0.99 [0.76, 1.28]
Total (95% CI)		**3128**		**3100**	**100.0%**	**0.99 [0.85, 1.14]**
Total events	326		326			

Heterogeneity: Chi² = 11.83, df = 12 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

Oral NAC + sodium chloride 0.9% vs sodium bicarbonate

Figure 18: CI-AKI (as reported by study)

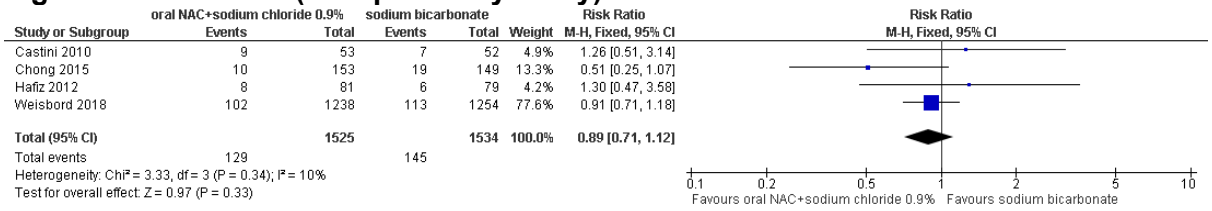
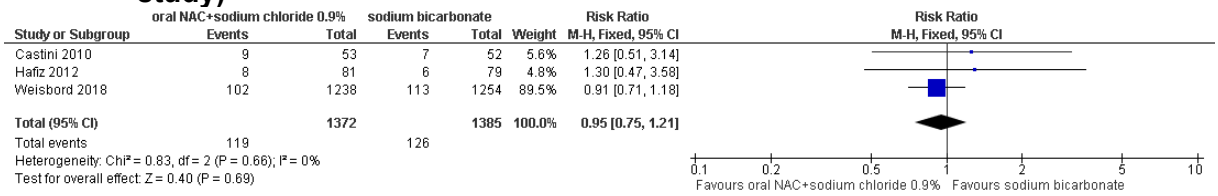


Figure 19: Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.9% vs sodium bicarbonate for CI-AKI (as reported by study)



Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate

Figure 20: CI-AKI (as reported by study)

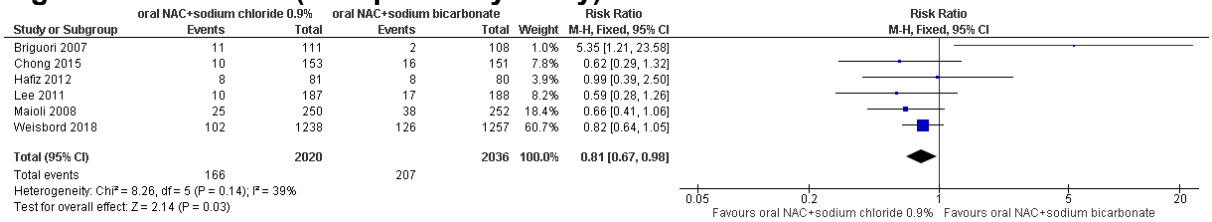
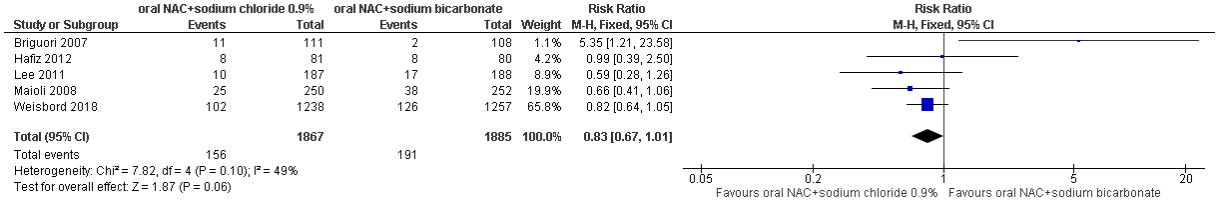
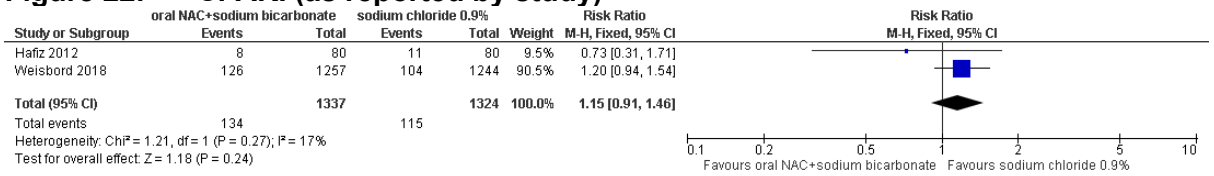


Figure 21: Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate for CI-AKI (as reported by study)



Oral NAC + sodium bicarbonate vs sodium chloride 0.9%

Figure 22: CI-AKI (as reported by study)



Oral NAC + sodium bicarbonate vs sodium bicarbonate

Figure 23: CI-AKI (as reported by study)

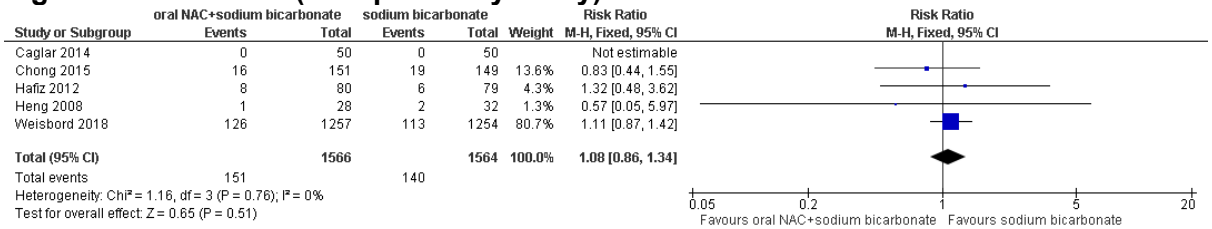
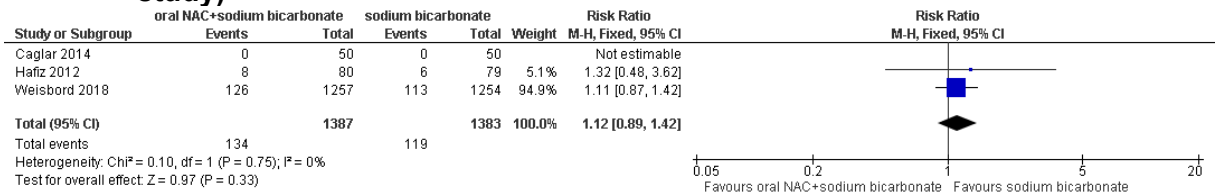
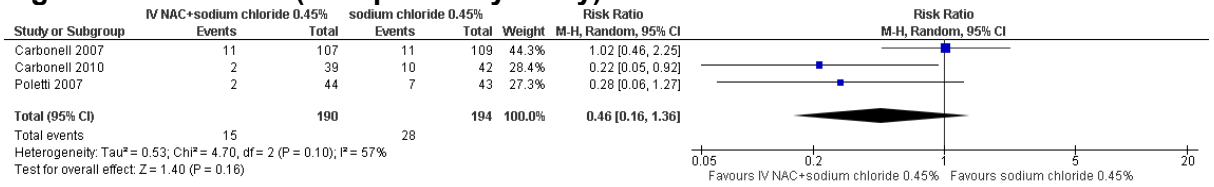


Figure 24: Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium bicarbonate vs sodium bicarbonate for CI-AKI (as reported by study)



IV NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Figure 25: CI-AKI (as reported by study)



IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Figure 26: CI-AKI (as reported by study)

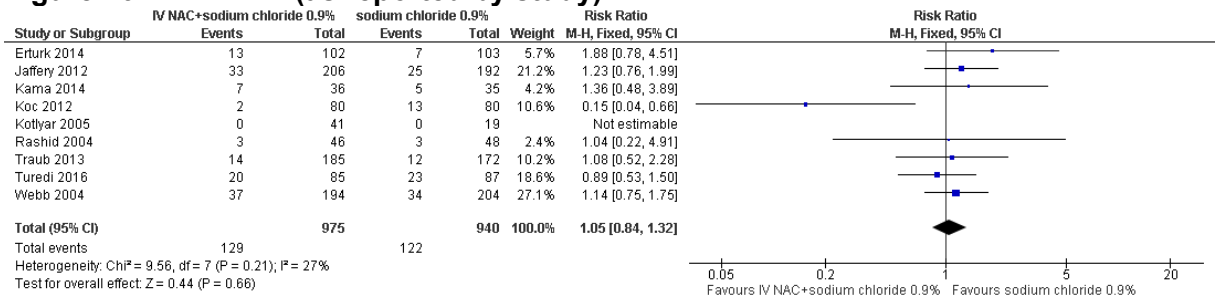


Figure 27: Funnel plot for IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% for CI-AKI (as reported by study)

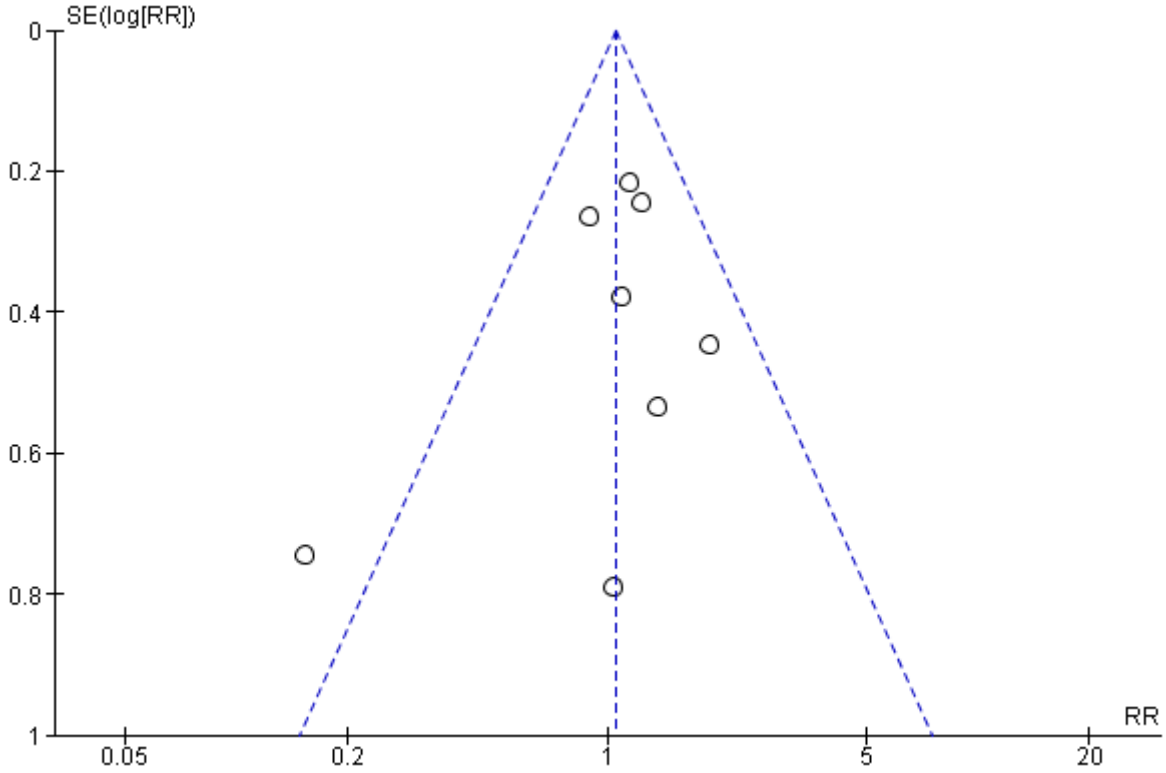
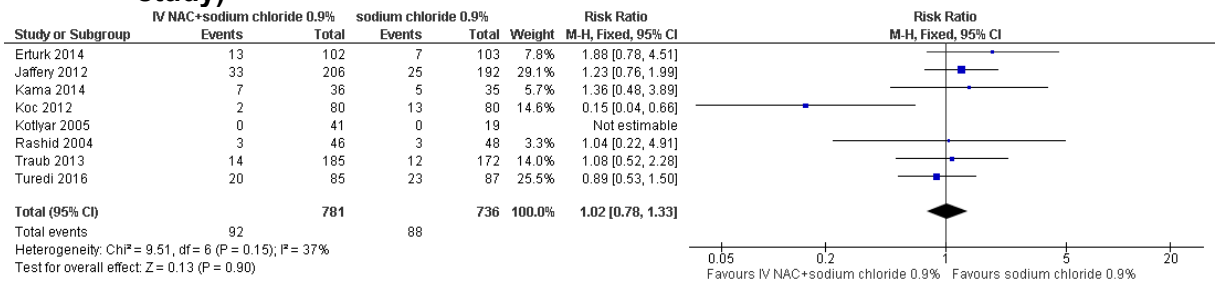


Figure 28: Sensitivity analysis excluding studies with a high risk of bias: IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% for CI-AKI (as reported by study)

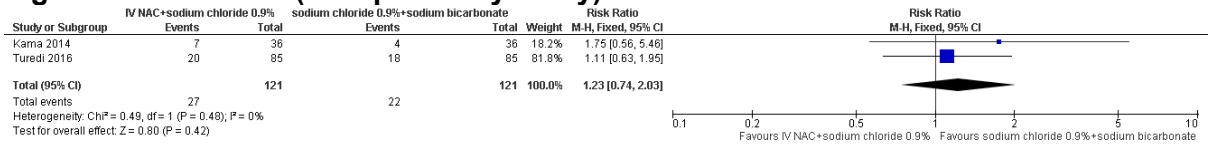


Study or Subgroup	IV NAC+sodium chloride 0.9% Events	Total	sodium chloride 0.9% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Erturk 2014	13	102	7	103	7.8%	1.88 [0.78, 4.51]
Jaffery 2012	33	206	25	192	29.1%	1.23 [0.76, 1.99]
Kama 2014	7	36	5	35	5.7%	1.36 [0.48, 3.89]
Koc 2012	2	80	13	80	14.6%	0.15 [0.04, 0.66]
Kotlyar 2005	0	41	0	19		Not estimable
Rashid 2004	3	46	3	48	3.3%	1.04 [0.22, 4.91]
Traub 2013	14	185	12	172	14.0%	1.08 [0.52, 2.28]
Turedi 2016	20	85	23	87	25.5%	0.89 [0.53, 1.50]
Total (95% CI)		**781**		**736**	**100.0%**	**1.02 [0.78, 1.33]**
Total events	92		88			

Heterogeneity: Chi² = 9.51, df = 6 (P = 0.15); I² = 37%
Test for overall effect: Z = 0.13 (P = 0.90)

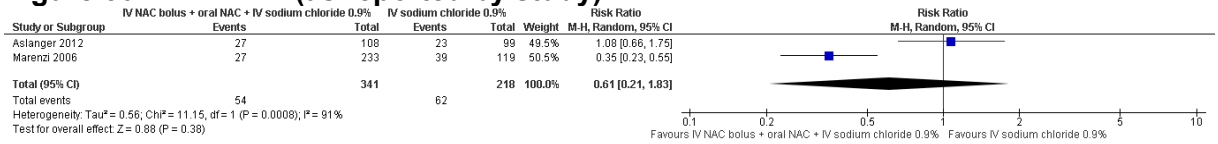
IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate

Figure 29: CI-AKI (as reported by study)



IV NAC bolus + oral NAC + IV sodium chloride 0.9% vs IV sodium chloride 0.9%

Figure 30: CI-AKI (as reported by study)



Appendix G – Network meta-analysis results

Model fit statistics

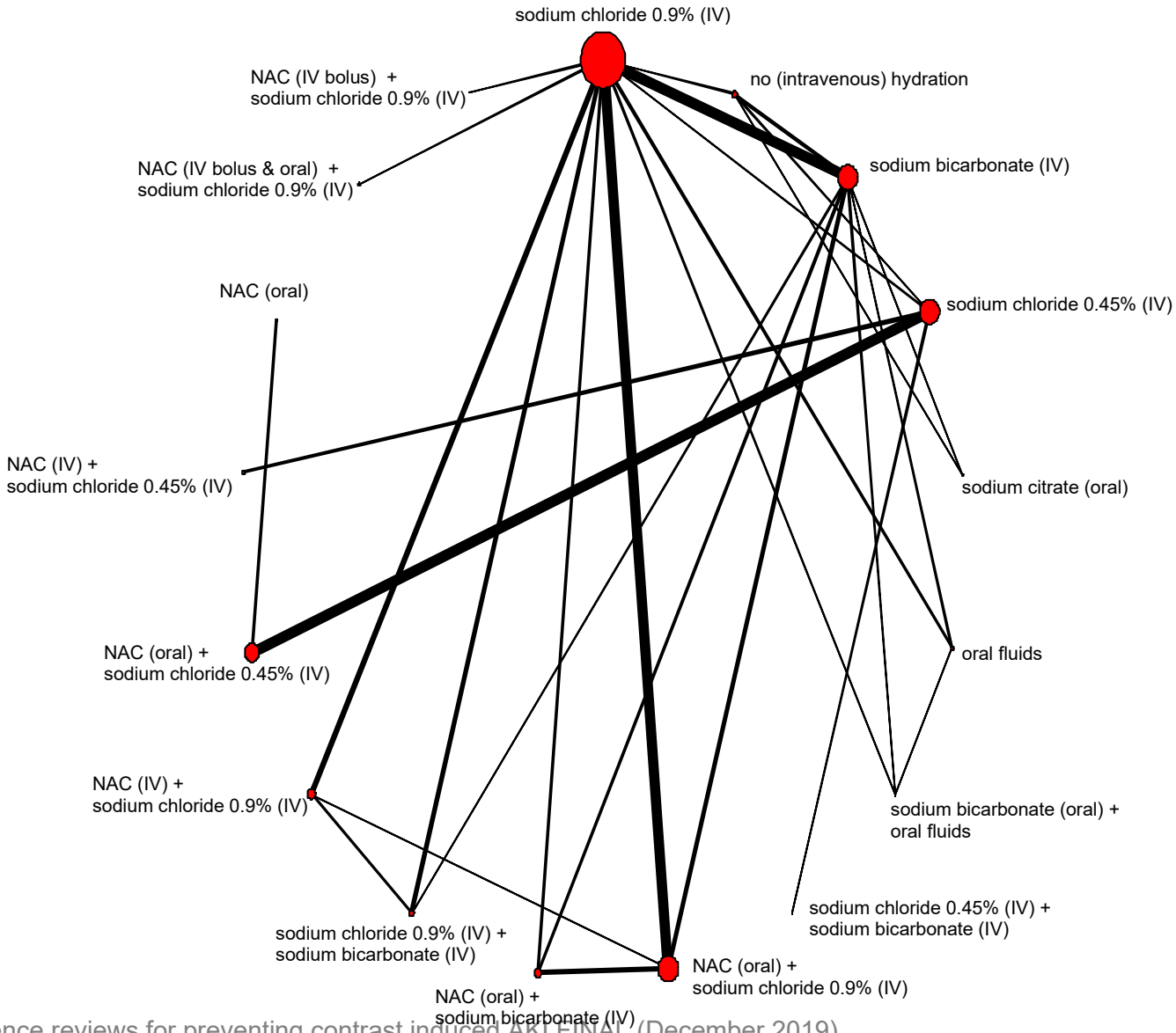
Table 11: Model fit statistics

Number of studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data points	Between study SD (95% CrI)	Preferred model
70	CI-AKI[a]	FE	880.858	220.1	153	---	RE
		RE	857.243	166.6		0.47 (0.26, 0.72)	

(a) CI-AKI: contrast-induced acute kidney injury.

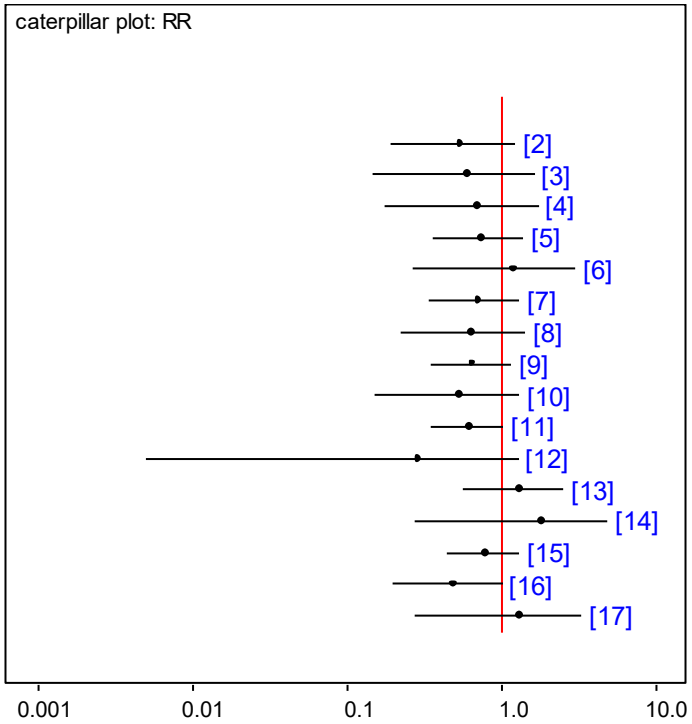
Figure 31: Network diagram

The thickness of the line represents the number of studies



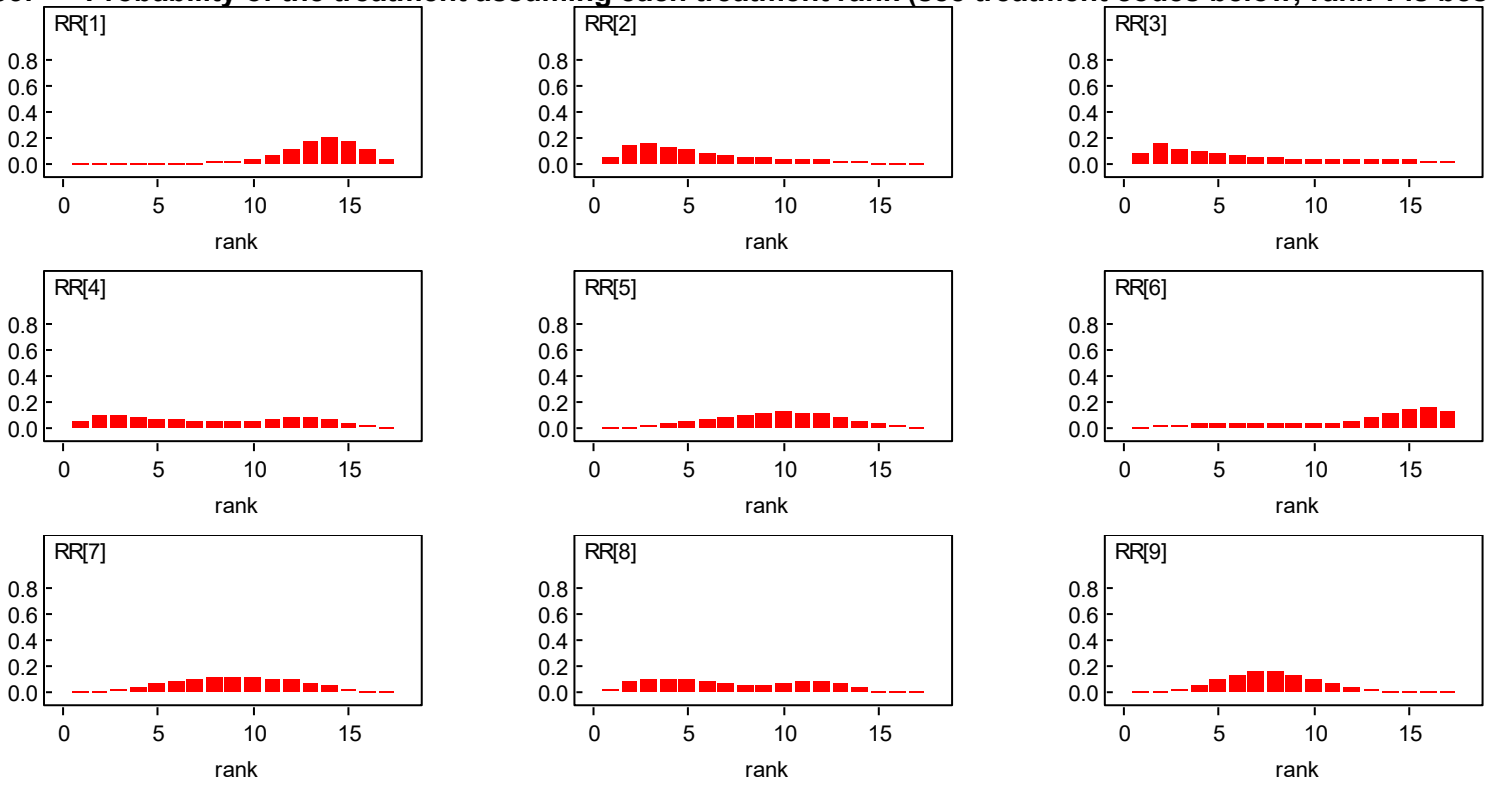
Caterpillar plot

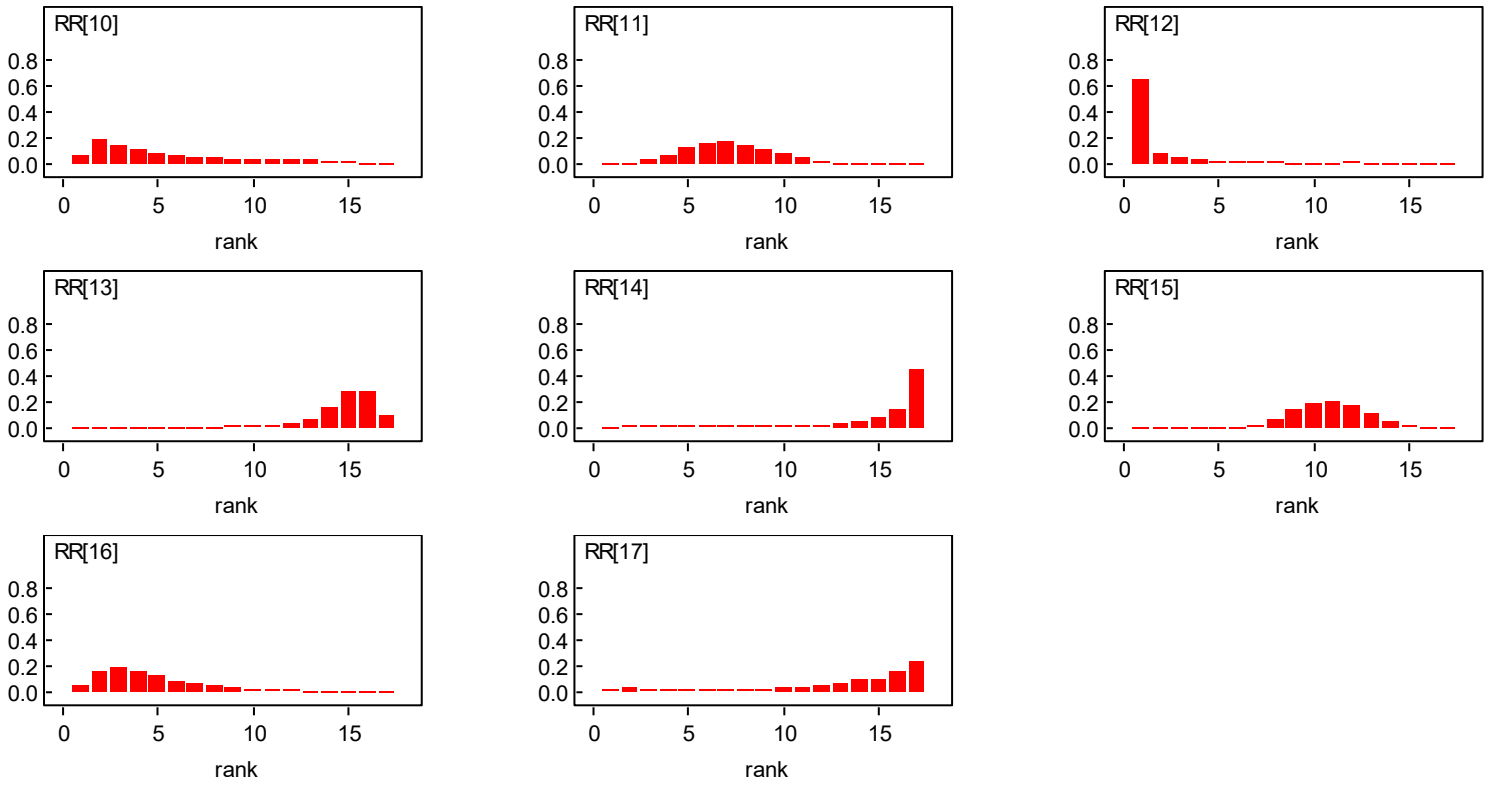
Figure 32: Relative effectiveness of all options versus no (intravenous) hydration. (Mean differences with 95% credible intervals and line of no effect in red; values higher than 1.0 favour no (intravenous) hydration; values lower than 1.0 favour the other treatments.)



Rank probability histograms

Figure 33: Probability of the treatment assuming each treatment rank (see treatment codes below; rank 1 is best)




RR[10]
RR[11]
RR[12]
RR[13]
RR[14]
RR[15]
RR[16]
RR[17]
0.0
0.2
0.4
0.6
0.8
0
5
10
15
rank

Treatment codes:

1 no (intravenous) hydration

2 NAC (IV bolus & oral) + sodium chloride 0.9% (IV)

3 NAC (IV bolus) + sodium chloride 0.9% (IV)

4 NAC (IV) + sodium chloride 0.45% (IV)

5 NAC (IV) + sodium chloride 0.9% (IV)

6 NAC (oral)

7 NAC (oral) + sodium bicarbonate (IV)

8 NAC (oral) + sodium chloride 0.45% (IV)

9 NAC (oral) + sodium chloride 0.9% (IV)

10 oral fluids

11 sodium bicarbonate (IV)

12 sodium bicarbonate (oral) + oral fluids

13 sodium chloride 0.45% (IV)

14 sodium chloride 0.45% (IV) + sodium bicarbonate (IV)

15 sodium chloride 0.9% (IV)

16 sodium chloride 0.9% (IV) + sodium bicarbonate (IV)

17 sodium citrate (oral)

Relative effectiveness

Table 12: Relative effectiveness of all pairwise combinations. (Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs less than 1 favour the column defining treatment, RRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	no (intravenous) hydration	NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	NAC (IV bolus) + sodium chloride 0.9% (IV)	NAC (IV) + sodium chloride 0.45% (IV)	NAC (IV) + sodium chloride 0.9% (IV)	NAC (oral)	NAC (oral) + sodium bicarbonate (IV)	NAC (oral) + sodium chloride 0.45% (IV)	NAC (oral) + sodium chloride 0.9% (IV)	oral fluids	sodium bicarbonate (IV)	sodium bicarbonate (oral) + oral fluids	sodium chloride 0.45% (IV)	sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	sodium chloride 0.9% (IV)	sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	sodium citrate (oral)
no (intravenous) hydration		---	---	---	---	---	---	---	---	---	0.51 (0.33, 0.78)	---	0.96 (0.54, 1.68)	---	0.86 (0.6, 1.24)	---	1.28 (0.37, 4.45)
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	0.49 (0.19, 1.24)		---	---	---	---	---	---	---	---	---	---	---	---	1.64 (0.55, 4.76)*	---	---

NAC (IV bolus) + sodium chloride 0.9% (IV)	0.50 (0.15, 1.64)	1.04 (0.27, 3.75)		---	---	---	---	---	---	---	---	---	---	1.43 (0.82, 2.5)*	---	---
NAC (IV) + sodium chloride 0.45% (IV)	0.60 (0.18, 1.75)	1.24 (0.29, 4.66)	1.20 (0.23, 5.68)		---	---	---	---	---	---	---	---	2.17 (0.74, 6.25)*	---	---	---	---
NAC (IV) + sodium chloride 0.9% (IV)	0.70 (0.36, 1.39)	1.44 (0.62, 3.42)	1.38 (0.46, 4.57)	1.16 (0.36, 4.35)		---	---	---	1.08 (0.53, 2.18)	---	0.81 (0.49, 1.35)*	---	---	---	0.95 (0.76, 1.19)*	---	---
NAC (oral)	1.03 (0.27, 3.05)	2.10 (0.44, 7.94)	2.02 (0.36, 9.73)	1.68 (0.46, 5.94)	1.47 (0.35, 4.59)		---	0.62 (0.45, 0.88)	---	---	---	---	---	---	---	---	---

NAC (oral) + sodium bicarbonate (IV)	0.67 (0.34, 1.33)	1.38 (0.57, 3.32)	1.33 (0.43, 4.43)	1.11 (0.35, 4.13)	0.96 (0.53, 1.72)	0.65 (0.21, 2.75)		---	0.81 (0.67, 0.98)	---	0.93 (0.75, 1.16)*	---	---	---	0.87 (0.69, 1.1)*	---	---
NAC (oral) + sodium chloride 0.45% (IV)	0.59 (0.22, 1.42)	1.20 (0.35, 3.93)	1.16 (0.27, 4.90)	0.96 (0.40, 2.54)	0.84 (0.29, 2.24)	0.57 (0.25, 1.50)	0.87 (0.30, 2.39)		---	---	---	---	2.00 (1.43, 2.70)*	---	---	---	---
NAC (oral) + sodium chloride 0.9% (IV)	0.61 (0.36, 1.15)	1.27 (0.58, 2.93)	1.22 (0.42, 3.97)	1.02 (0.34, 3.74)	0.88 (0.56, 1.45)	0.60 (0.20, 2.48)	0.92 (0.62, 1.44)	1.06 (0.42, 3.00)		---	1.12 (0.89, 1.41)*	---	---	---	1.04 (0.91, 1.20)*	---	---
oral fluids	0.47 (0.15, 1.32)	0.96 (0.28, 3.10)	0.93 (0.22, 3.86)	0.78 (0.18, 3.62)	0.67 (0.23, 1.75)	0.46 (0.11, 2.32)	0.70 (0.24, 1.87)	0.80 (0.21, 3.03)	0.76 (0.27, 1.89)		2.1 (0.2, 21.42)	1.05 (0.07, 15.69)	---	---	1.52 (0.72, 3.2)	---	---

sodium bicarbonate (IV)	0.59 (0.35, 1.04)	1.22 (0.54, 2.79)	1.18 (0.40, 3.74)	0.98 (0.33, 3.50)	0.85 (0.52, 1.39)	0.58 (0.19, 2.33)	0.88 (0.56, 1.43)	1.02 (0.40, 2.80)	0.96 (0.65, 1.37)	1.26 (0.51, 3.47)		0.5 (0.05, 5.0)*	---	---	1.04 (0.88, 1.23)	4.14 (0.96, 17.87)	1.67 (0.42, 6.67)*
sodium bicarbonate (oral) + oral fluids	0.17 (0.00, 1.30)	0.34 (0.01, 2.89)	0.33 (0.01, 3.27)	0.27 (0.01, 2.93)	0.24 (0.01, 1.80)	0.16 (0.00, 1.83)	0.25 (0.01, 1.88)	0.28 (0.01, 2.63)	0.27 (0.01, 1.97)	0.36 (0.01, 2.98)	0.28 (0.01, 2.04)		---	---	4.67 (0.61, 35.84)	---	---
sodium chloride 0.45% (IV)	1.23 (0.57, 2.53)	2.52 (0.85, 7.20)	2.42 (0.66, 9.23)	2.01 (0.96, 4.98)	1.76 (0.72, 3.96)	1.19 (0.51, 3.51)	1.83 (0.75, 4.20)	2.09 (1.37, 3.37)	2.00 (0.85, 4.11)	2.61 (0.81, 8.87)	2.08 (0.92, 4.36)	7.37 (0.88, 245.40)		1.25 (0.37, 4.28)	0.36 (0.13, 1.0)	---	---
sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	1.53 (0.28, 4.92)	3.12 (0.48, 12.49)	2.97 (0.41, 15.08)	2.46 (0.47, 10.53)	2.20 (0.37, 7.21)	1.47 (0.26, 6.92)	2.29 (0.39, 7.46)	2.56 (0.55, 8.71)	2.50 (0.43, 7.46)	3.23 (0.47, 14.98)	2.59 (0.45, 8.03)	8.98 (0.67, 339.30)	1.24 (0.27, 3.58)		---	---	---

sodium chloride 0.9% (IV)	0.74 (0.45, 1.32)	1.54 (0.74, 3.37)	1.48 (0.53, 4.61)	1.24 (0.42, 4.41)	1.07 (0.73, 1.62)	0.73 (0.25, 2.94)	1.11 (0.73, 1.79)	1.28 (0.52, 3.49)	1.21 (0.91, 1.61)	1.59 (0.67, 4.28)	1.26 (0.95, 1.73)	4.43 (0.63, 145.70)	0.61 (0.30, 1.36)	0.48 (0.16, 2.78)		0.46 (0.19, 1.11)	---
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	0.45 (0.20, 1.02)	0.93 (0.35, 2.48)	0.90 (0.27, 3.20)	0.75 (0.22, 3.02)	0.65 (0.33, 1.24)	0.44 (0.13, 1.97)	0.68 (0.32, 1.43)	0.78 (0.26, 2.47)	0.74 (0.36, 1.40)	0.97 (0.33, 3.05)	0.77 (0.39, 1.46)	2.71 (0.34, 91.26)	0.37 (0.14, 0.99)	0.30 (0.08, 1.86)	0.61 (0.32, 1.09)		---
sodium citrate (oral)	1.13 (0.27, 3.30)	2.31 (0.45, 8.75)	2.20 (0.37, 10.71)	1.85 (0.33, 9.33)	1.62 (0.36, 5.06)	1.09 (0.19, 5.98)	1.69 (0.38, 5.24)	1.91 (0.37, 7.83)	1.84 (0.42, 5.30)	2.39 (0.44, 10.47)	1.91 (0.45, 5.54)	6.70 (0.58, 252.60)	0.92 (0.19, 3.23)	0.74 (0.12, 5.36)	1.52 (0.35, 4.36)	2.48 (0.52, 8.63)	

** RR and 95% CI were inverted to match the direction of the comparison between 'treatment' and 'control'. For example: IV NAC bolus + oral NAC + sodium chloride 0.9% was the 'treatment' and sodium chloride 0.9% (IV) was the 'control' reported by Aslanger 2012 and Marenzi 2006. In this relative effectiveness table, the column defines the 'treatment' and the row defines the 'control (sodium chloride 0.9% (IV) becomes the 'treatment' and IV NAC bolus + oral NAC + sodium chloride 0.9% the control).*

Appendix H – GRADE tables

Pair-wise meta-analysis

Sodium chloride 0.45% vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.45%	No (intravenous) hydration	Relative (95% CI)	Absolute	
CI-AKI (as reported by study) - sCr <132.6µmol/l											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/330 (6.7%)	23/330 (7%)	RR 0.96 (0.54 to 1.68)	0 fewer per 100 (from 3 fewer to 5 more)	VERY LOW

[1] Chen 2008
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium chloride 0.9% vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	No (intravenous) hydration	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	42/446 (9.4%)	49/457 (10.7%)	RR 0.86 (0.6 to 1.24)	2 fewer per 100 (from 4 fewer to 3 more)	LOW

[1] Maioli 2011; Nijssen 2017
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Subgroup analyses (outcome: CI-AKI): Sodium chloride 0.9% vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	No (intravenous) hydration (diabetes)	Relative (95% CI)	Absolute	
Subgroup: diabetes											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/31 (35.5%)	10/34 (29.4%)	RR 1.21 (0.6 to 2.44)	6 more per 100 (from 12 fewer to 42 more)	VERY LOW
Subgroup: older people >75 years											
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/36 (41.7%)	11/29 (37.9%)	RR 1.10 (0.6 to 2.01)	4 more per 100 (from 15 fewer to 38 more)	VERY LOW

[1] Maioli 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Maioli 2011 reported older people ≥75 years

Other outcomes: Sodium chloride 0.9% vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	No (intravenous) hydration	Relative (95% CI)	Absolute	
Mortality: in-hospital mortality											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/150 (3.3%)	8/150 (5.3%)	RR 0.62 (0.21 to 1.87)	2 fewer per 100 (from 4 fewer to 5 more)	VERY LOW
Mortality: all-cause mortality											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/328 (0%)	3/332 (0.9%)	RR 0.14 (0.01 to 2.79)	1 fewer per 100 (from 1 fewer to 2 more)	LOW
Need for renal replacement therapy: dialysis											
6	randomised trials[5]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	28/2441 (1.1%)	27/2468 (1.1%)	RR 1.04 (0.62 to 1.75)	0 more per 100 (from 0 fewer to 1 more)	LOW
Adverse events											
2	randomised trials[1,6]	serious[2]	very serious[7]	no serious indirectness	very serious[3]	none	32/478 (6.7%)	15/482 (3.1%)	RR 4.59 (0.16 to 134.39)	11 more per 100 (from 3 fewer to 100 more)	VERY LOW

[1] Maioli 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Nijssen 2017; all-cause mortality within 35 days post-contrast
[5] Akyuz 2014; Brar 2008; Masuda 2007; Mueller 2002; Solomon 2015; Weisbord 2018
[6] Maioli 2011 (major adverse cardiovascular events: death, recurrent myocardial infarction, repeated urgent PCI, stroke and major bleeding); Nijssen 2017 (symptomatic heart failure)
[7] i-squared >66.7%; random effects model was used to account for heterogeneity

Sodium chloride 0.9% vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Oral fluids**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

3	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/188 (9%)	11/188 (5.9%)	RR 1.52 (0.72 to 3.2)	3 more per 100 (from 2 fewer to 13 more)	VERY LOW

[1] Akyuz 2014; Cho 2010; Wrobel 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Sodium chloride 0.9% vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Oral fluids**	**Relative (95% CI)**	**Absolute**	
Mortality: all-cause mortality											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/109 (0.92%)	0/116 (0%)	RR 3.19 (0.13 to 77.5)	-	VERY LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/109 (0.92%)	0/116 (0%)	RR 3.19 (0.13 to 77.5)	-	VERY LOW
Length of hospital stay in days (Better indicated by lower values)											
1	randomised trials[5]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	27	22	-	MD 0.38 lower (3.81 lower to 3.05 higher)	VERY LOW

[1] Akyuz 2014; mortality at 30 days
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Akyuz 2014
[5] Cho 2010

Sensitivity analysis excluding studies with a high risk of bias: Sodium chloride 0.9% vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	Oral fluids	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
2	randomised trials[1]	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	14/136 (10.3%)	9/138 (6.5%)	RR 1.54 (0.68 to 3.51)	4 more per 100 (from 2 fewer to 16 more)	VERY LOW

[1] Akyuz 2014; Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] i-squared >33.3%
[4] 95% confidence interval crosses both ends of a defined MID interval

Sodium chloride 0.9% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	Sodium chloride 0.45%	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/685 (0.73%)	14/698 (2%)	RR 0.36 (0.13 to 1)	1 fewer per 100 (from 2 fewer to 0 more)	VERY LOW

[1] Mueller 2002
[2] 33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Subgroup analyses (outcome: CI-AKI): Sodium chloride 0.9% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Sodium chloride 0.45%**	**Relative (95% CI)**	**Absolute**	
Subgroup: chronic kidney disease											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/138 (2.2%)	6/148 (4.1%)	RR 0.54 (0.14 to 2.10)	2 fewer per 100 (from 3 fewer to 4 more)	VERY LOW
Subgroup: diabetes											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/107 (0%)	6/110 (5.5%)	RR 0.08 (0.0 to 1.39)	5 fewer per 100 (from 5 fewer to 2 more)	VERY LOW
Subgroup: low volume of contrast agent											
1	randomised trials[4]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/434 (1.2%)	6/430 (1.4%)	RR 0.83 (0.25 to 2.69)	0 fewer per 100 (from 1 fewer to 2 more)	VERY LOW
Subgroup: high volume of contrast agent											
1	randomised trials[5]	very serious[2]	no serious inconsistency	no serious indirectness	serious[6]	none	0/251 (0%)	8/268 (3%)	RR 0.06 (0.0 to 1.08)	28 fewer per 1000 (from 30 fewer to 2 more)	VERY LOW

[1] Mueller 2002
[2] 33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Mueller 2002 reported low volume of contrast agent <250ml
[5] Mueller reported high volume of contrast agent ≥250 ml
[6] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Sodium chloride 0.9% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	Sodium chloride 0.45%	Relative (95% CI)	Absolute	
Mortality											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/265 (0.38%)	3/265 (1.1%)	RR 0.33 (0.03 to 3.18)	1 fewer per 100 (from 1 fewer to 2 more)	VERY LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[4]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/685 (0.15%)	1/698 (0.14%)	RR 1.02 (0.06 to 16.26)	0 more per 100 (from 0 fewer to 2 more)	VERY LOW
Adverse events											
1	randomised trials[5]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/265 (5.3%)	17/265 (6.4%)	RR 0.82 (0.41 to 1.64)	1 fewer per 100 (from 4 fewer to 4 more)	VERY LOW

[1] Mueller 2002; mortality within 30 days in subgroup of people receiving coronary artery stents
[2] 33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Mueller 2002
[5] Mueller 2002; major adverse cardiac events within 30 days in a predefined subgroup of 530 patients receiving coronary artery stents

Sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9%	Sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											

15	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	262/2716 (9.6%)	249/2696 (9.2%)	RR 1.04 (0.88 to 1.23)	0 more per 100 (from 1 fewer to 2 more)	MODERATE

[1] Adolph 2008; Boucek 2013; Brar 2008; Castini 2010; Cho 2010; Hafiz 2012; Kooiman 2014a; Kooiman 2018; Maioli 2011; Masuda 2007; Merten 2004; Nieto-Rios 2014; Solomon 2015; van Mourik 2018; Weisbord 2018
[2] i-squared >33.3%

Other outcomes: Sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	
Mortality: all-cause mortality (30 days)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/178 (1.7%)	3/175 (1.7%)	RR 0.98 (0.2 to 4.8)	0 fewer per 100 (from 1 fewer to 7 more)	VERY LOW
Mortality: all-cause mortality (>30 days)											
3	randomised trials[4]	no serious risk of bias	serious[5]	no serious indirectness	very serious[3]	none	51/1618 (3.2%)	44/1624 (2.7%)	RR 1.36 (0.65 to 2.83)	1 more per 100 (from 1 fewer to 5 more)	VERY LOW
Mortality: in-hospital mortality											
2	randomised trials[6]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/179 (3.9%)	3/180 (1.7%)	RR 2.05 (0.57 to 7.35)	2 more per 100 (from 1 fewer to 11 more)	VERY LOW
Need for renal replacement therapy											
4	randomised trials[7]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	24/1647 (1.5%)	26/1654 (1.6%)	RR 0.93 (0.54 to 1.61)	0 fewer per 100 (from 1 fewer to 1 more)	LOW
Adverse events											

3	randomised trials[8]	serious[2]	no serious inconsistency	no serious indirectness	serious[9]	none	26/387 (6.7%)	15/386 (3.9%)	RR 1.74 (0.94 to 3.21)	3 more per 100 (from 0 fewer to 9 more)	LOW
Adverse events: heart failure											
3	randomised trials[10]	very serious[11]	serious[5]	no serious indirectness	very serious[3]	none	24/431 (5.6%)	14/414 (3.4%)	RR 1.80 (0.59 to 5.48)	3 more per 100 (from 1 fewer to 15 more)	VERY LOW
Length of hospital stay in days (Better indicated by lower values)											
2	randomised trials[12]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	91	83	-	MD 0.06 lower (2.3 lower to 2.18 higher)	VERY LOW

[1] Brar 2008
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Brar 2008 (30 days to 6 months); Solomon 2015 (6 months): Weisbord 2018 (3 months)
[5] i-squared >33.3%
[6] Maioli 2011; Masuda 2007
[7] Brar 2008 (dialysis); Masuda 2007 (hemodialysis); Solomon 2015 (dialysis); Weisbord 2018 (dialysis)
[8] Boucek 2013 (any adverse events); Brar 2008 (mycardial infarction, cerebrovascular accident [stroke and transient ischemic attack]); Maioli 2011 (major adverse cardiovascular events: death, recurrent myocardial infarction, repeated urgent PCI, stroke & major bleeding)
[9] 95% confidence interval crosses one end of a defined MID interval
[10] Kooiman 2014 (acute heart failure); Masuda 2007 (heart failure); Nieto-Rios 2014 (decompensated heart failure)
[11] >33.3% of weighted data from studies at high risk of bias
[12] Boucek 2013; Cho 2010

Sensitivity analysis excluding studies with a high risk of bias: Sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

14	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	252/2687 (9.4%)	247/2666 (9.3%)	RR 1.01 (0.85 to 1.19)	0 more per 100 (from 1 fewer to 2 more)	HIGH

[1] Adolph 2008; Boucek 2013; Brar 2008; Castini 2010; Cho 2010; Hafiz 2012; Kooiman 2014a; Kooiman 2018; Maioli 2011; Merten 2004; Nieto-Rios 2014; Solomon 2015; van Mourik 2018; Weisbord 2018

Sodium chloride 0.9% vs oral sodium bicarbonate + oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV sodium chloride 0.9%**	**Oral sodium bicarbonate + oral fluids**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/27 (22.2%)	1/21 (4.8%)	RR 4.67 (0.61 to 35.84)	17 more per 100 (from 2 fewer to 100 more)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Sodium chloride 0.9% vs oral sodium bicarbonate + oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9%**	**Oral sodium bicarbonate + oral fluids**	**Relative (95% CI)**	**Absolute**	
Length of hospital stay in days (Better indicated by lower values)											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	27	21	-	MD 2.72 lower (7.25 lower to 1.81 higher)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium chloride 0.9% (5 hours) vs sodium chloride 0.9% (20 hours)

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9% (5 hours)**	**Sodium chloride 0.9% (20 hours)**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/60 (3.3%)	2/62 (3.2%)	RR 1.03 (0.15 to 7.1)	0 more per 100 (from 3 fewer to 20 more)	VERY LOW

[1] Torigoe 2013
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium chloride 0.45% + sodium bicarbonate vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.45% + sodium bicarbonate**	**Sodium chloride 0.45%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/36 (13.9%)	4/36 (11.1%)	RR 1.25 (0.37 to 4.28)	3 more per 100 (from 7 fewer to 36 more)	VERY LOW

[1] Vasheghani-Farahani 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9% + sodium bicarbonate**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
4	randomised trials[1]	serious[2]	serious[3]	no serious indirectness	serious[4]	none	25/271 (9.2%)	47/271 (17.3%)	RR 0.46 (0.19 to 1.11)	9 fewer per 100 (from 14 fewer to 2 more)	VERY LOW

[1] Kama 2014; Motohiro 2011; Tamura 2009; Turedi 2016
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] i-squared >33.3%
[4] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Sodium chloride 0.9% + sodium bicarbonate vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9% + sodium bicarbonate**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
Mortality: in-hospital mortality											

1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/85 (11.8%)	12/87 (13.8%)	RR 0.85 (0.39 to 1.87)	2 fewer per 100 (from 8 fewer to 12 more)	LOW
Need for renal replacement therapy											
3	randomised trials[3]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/193 (5.7%)	16/194 (8.2%)	RR 0.72 (0.36 to 1.44)	2 fewer per 100 (from 5 fewer to 4 more)	LOW
Adverse events											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/72 (0%)	1/72 (1.4%)	RR 0.33 (0.01 to 8.05)	1 fewer per 100 (from 1 fewer to 10 more)	LOW

[1] Turedi 2016
[2] 95% confidence interval crosses both ends of a defined MID interval
[3] Kama 2014 (type of RRT was not reported); Tamura 2009 (hemodialysis); Turedi 2016 (hemodialysis or peritoneal dialysis)
[4] Tamura 2009 (adverse clinical events within first 7 days after procedure)

Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium chloride 0.9% + sodium bicarbonate**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/29 (27.6%)	2/30 (6.7%)	RR 4.14 (0.96 to 17.87)	21 more per 100 (from 0 fewer to 100 more)	LOW

[1] Ueda 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Sodium chloride 0.9% + sodium bicarbonate vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium chloride 0.9% + sodium bicarbonate	Sodium bicarbonate	Relative (95% CI)	Absolute	
Mortality: in-hospital mortality											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/29 (6.9%)	3/30 (10%)	RR 0.69 (0.12 to 3.83)	3 fewer per 100 (from 9 fewer to 28 more)	VERY LOW
Adverse events											
1	randomised trials[1,4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/29 (34.5%)	9/30 (30%)	RR 1.15 (0.55 to 2.41)	4 more per 100 (from 14 fewer to 42 more)	VERY LOW
Length of hospital stay in days (Better indicated by lower values)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	30	30	-	MD 1.40 lower (10.90 lower to 8.10 higher)	VERY LOW

[1] Ueda 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Overall adverse events: congestive heart failure, acute renal failure requiring dialysis, lethal arrythmia and death

Oral sodium bicarbonate + oral fluids vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral sodium bicarbonate + oral fluids	Oral fluids	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/21 (4.8%)	1/22 (4.5%)	RR 1.05 (0.07 to 15.69)	0 more per 100 (from 4 fewer to 67 more)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Oral sodium bicarbonate + oral fluids vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral sodium bicarbonate + oral fluids**	**Oral fluids**	**Relative (95% CI)**	**Absolute**	
Length of hospital stay (Better indicated by lower values)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	22	-	MD 2.54 higher (2.32 lower to 7.40 higher)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium bicarbonate vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium bicarbonate**	**No (intravenuos) hydration**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

3	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/263 (9.9%)	51/259 (19.7%)	RR 0.51 (0.33 to 0.78)	10 fewer per 100 (from 4 fewer to 13 fewer)	MODERATE

[1] Kooiman 2014b; Maioli 2011; Martin-Moreno 2015

[2] >33.3% of weighted data from studies at moderate or high risk of bias

Subgroup analyses (outcome: CI-AKI): Sodium bicarbonate vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium bicarbonate**	**No (intravenous) hydration**	**Relative (95% CI)**	**Absolute**	
Subgroup: diabetes											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/31 (16.1%)	10/34 (29.4%)	RR 0.55 (0.21 to 1.43)	13 fewer per 100 (from 23 fewer to 13 more)	VERY LOW
Subgroup: older people >75 years											
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	8/38 (21.1%)	11/29 (37.9%)	RR 0.56 (0.26 to 1.2)	17 fewer per 100 (from 28 fewer to 8 more)	LOW

[1] Maioli 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Maioli 2011 reported older people ≥75 years
[5] 95% confidence interval crosses one end of a defined MID interval

Sensitivity analysis excluding studies with a high risk of bias: Sodium bicarbonate vs no (intravenous) hydration

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium bicarbonate	No (intravenous) hydration	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/220 (10.5%)	47/215 (21.9%)	RR 0.48 (0.31 to 0.77)	11 fewer per 100 (from 5 fewer to 15 fewer)	MODERATE

[1] Kooiman 2014b; Maioli 2011
[2] >33.3% of weighted data from studies at moderate or high risk of bias

Sodium bicarbonate vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium bicarbonate	Oral fluids	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/21 (9.5%)	1/22 (4.5%)	RR 2.1 (0.2 to 21.42)	5 more per 100 (from 4 fewer to 93 more)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Sodium bicarbonate vs oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium bicarbonate	Oral fluids	Relative (95% CI)	Absolute	

Length of hospital stay in days (Better indicated by lower values)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	22	-	MD 0.27 lower (3.48 lower to 2.94 higher)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium bicarbonate vs oral sodium citrate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium bicarbonate**	**Oral sodium citrate**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/43 (7%)	5/43 (11.6%)	RR 0.6 (0.15 to 2.36)	5 fewer per 100 (from 10 fewer to 16 more)	VERY LOW

[1] Martin-Moreno 2015
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Sodium bicarbonate vs oral sodium bicarbonate + oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV sodium bicarbonate**	**Oral sodium bicarbonate + oral fluids**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/21 (9.5%)	1/21 (4.8%)	RR 2 (0.2 to 20.41)	5 more per 100 (from 4 fewer to 92 more)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Sodium bicarbonate vs oral sodium bicarbonate + oral fluids

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium bicarbonate**	**Oral sodium bicarbonate + oral fluids**	**Relative (95% CI)**	**Absolute**	
Length of hospital stay in days (Better indicated by lower values)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	27	21	-	MD 2.81 lower (7.10 lower to 1.48 higher)	VERY LOW

[1] Cho 2010
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Oral sodium citrate vs no (intravenous) hydration

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral sodium citrate**	**No (intravenuos) hydration**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											

1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/43 (11.6%)	4/44 (9.1%)	RR 1.28 (0.37 to 4.45)	3 more per 100 (from 6 fewer to 31 more)	VERY LOW

[1] Martin-Moreno 2015
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.45%**	**Sodium chloride 0.45%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
14	randomised trials[1]	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	49/583 (8.4%)	96/571 (16.8%)	RR 0.50 (0.37 to 0.70)	8 fewer per 100 (from 5 fewer to 11 fewer)	VERY LOW

[1] Agrawal 2004; Allaqaband 2002; Briguori 2002; Durham 2002; Goldenberg 2004; Hsu 2007; Izani Wan Mohamed 2008; Kitzler 2012; MacNeill 2003; Miner 2004; Oldemeyer 2003; Seyon 2007; Shyu 2002; Tepel 2000
[2] >33.3% of weighted data from studies at high risk of bias
[3] i-squared >33.3%

Subgroup analyses (outcome: CI-AKI): Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.45%**	**Sodium chloride 0.45% (CKD)**	**Relative (95% CI)**	**Absolute**	
Subgroup: chronic kidney disease											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/7 (42.9%)	5/12 (41.7%)	RR 1.03 (0.35 to 3.05)	1 more per 100 (from 27 fewer to 85 more)	VERY LOW
Subgroup: diabetes											
2	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/64 (20.3%)	8/58 (13.8%)	RR 1.5 (0.7 to 3.24)	7 more per 100 (from 4 fewer to 31 more)	VERY LOW

[1] Durham 2002
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Durham 2002, Allaqaband 2002

Other outcomes: Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.45%**	**Sodium chloride 0.45%**	**Relative (95% CI)**	**Absolute**	
Mortality: long-term mortality											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/95 (4.2%)	3/85 (3.5%)	RR 1.19 (0.27 to 5.18)	1 more per 100 (from 3 fewer to 15 more)	VERY LOW
Mortality: in-hospital mortality											
1	randomised trials[4]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/95 (0%)	2/85 (2.4%)	RR 0.18 (0.01 to 3.68)	2 fewer per 100 (from 2 fewer to 6 more)	VERY LOW
Need for renal replacement therapy: dialysis											
3	randomised trials[5]	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/247 (0.4%)	2/237 (0.84%)	RR 0.69 (0.13 to 3.52)	0 fewer per 100 (from 1 fewer to 2 more)	VERY LOW
Adverse events											

5	randomised trials[7]	very serious[2]	no serious inconsistency[8]	no serious indirectness	serious[3,9]	none	41/329 (12.5%)	23/307 (7.5%)	RR 1.61 (1.01 to 2.56)	5 more per 100 (from 0 more to 12 more)	VERY LOW
Length of hospital stay in days (Better indicated by lower values)											
2	randomised trials[10]	very serious[2]	serious[8]	no serious indirectness	very serious[3]	none	60	56	-	MD 1.24 lower (3.94 lower to 1.45 higher)	VERY LOW
Readmission for AKI											
1	randomised trials[4]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/95 (13.7%)	13/85 (15.3%)	RR 0.89 (0.44 to 1.82)	2 fewer per 100 (from 9 fewer to 13 more)	VERY LOW

[1] Miner 2004; long-term follow-up but time was not reported
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Miner 2004
[5] Briguori 2002; Miner 2004; Shyu 2002
[6] >33.3% of weighted data from studies at moderate or high risk of bias
[7] Goldenberg 2004 (congestive heart failure); Izani Wan Mahamed 2008 (adverse events); Miner 2004 (in-hospital adverse events and long-term clinical events but time was not reported); Oldemeyer 2003 (adverse events)
[8] i-squared >33.3%
[9] 95% confidence interval crosses one end of a defined MID interval
[10] Hsu 2007; Oldemeyer 2003

Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.45%**	**Sodium chloride 0.45%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
11	randomised trials[1]	serious[2]	serious[3]	no serious indirectness	serious[4]	none	39/456 (8.6%)	65/455 (14.3%)	RR 0.61 (0.42 to 0.88)	6 fewer per 100 (from 2 fewer to 8 fewer)	VERY LOW

[1] Agrawal 2004; Allaqaband 2002; Briguori 2002; Durham 2002; Goldenberg 2004; Izani Wan Mohamed 2008; Kitzler 2012; Oldemeyer 2003; Seyon 2007; Shyu 2002; Tepel 2000
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] i-squared >33.3%
[4] 95% confidence interval crosses one end of a defined MID interval

Oral NAC + sodium chloride 0.45% vs oral NAC

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.45%	Oral NAC	Relative (95% CI)	Absolute	
CI-AKI (as reported by study) - sCr ≥132.6µmol/l											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40/188 (21.3%)	64/188 (34%)	RR 0.62 (0.45 to 0.88)	13 fewer per 100 (from 4 fewer to 19 fewer)	VERY LOW

[1] Chen 2008
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Sodium chloride 0.9%	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
16	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	341/3307 (10.3%)	352/3290 (10.7%)	RR 0.96 (0.83 to 1.10)	0 fewer per 100 (from 2 fewer to 1 more)	MODERATE

[1] ACT investigators 2011; Albabtain 2013; Baskurt 2009; Castini 2010; Erturk 2014; Ferrario 2009; Fung 2004; Gomes 2005; Habib 2016; Hafiz 2012; Kay 2003; Khalili 2006; Reinecke 2007; Sadineni 2017; Saitoh; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

Subgroup analyses (outcome: CI-AKI): Oral NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.9%**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
Subgroup: chronic kidney disease											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/188 (6.4%)	10/179 (5.6%)	RR 1.14 (0.51 to 2.58)	1 more per 100 (from 3 fewer to 9 more)	LOW
Subgroup: diabetes											
5	randomised trials[3]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	110/797 (13.8%)	113/769 (14.7%)	RR 0.95 (0.75 to 1.21)	1 fewer per 100 (from 4 fewer to 3 more)	MODERATE
Subgroup: older people >75 years											
1	randomised trials[5]	very serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/7 (57.1%)	8/11 (72.7%)	RR 0.79 (0.38 to 1.64)	15 fewer per 100 (from 45 fewer to 47 more)	VERY LOW
Subgroup: low volume of contrast agent											
1	randomised trials[7]	very serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/7 (85.7%)	8/11 (72.7%)	RR 1.18 (0.74 to 1.89)	13 more per 100 (from 19 fewer to 65 more)	VERY LOW
Subgroup: high volume of contrast agent											
2	randomised trials[8]	very serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/66 (10.6%)	7/59 (11.9%)	RR 0.98 (0.35 to 2.72)	0 fewer per 100 (from 8 fewer to 20 more)	VERY LOW

[1] ACT investigators 2011
[2] 95% confidence interval crosses both ends of a defined MID interval

[3] ACT investigators 2011, Ferrario 2009; Fung 2004, Gomes 2005; Sadineni 2017
[4] 95% confidence interval crosses one end of a defined MID interval
[5] Sadineni 2017 reported older people >60 years
[6] >33.3% of weighted data from studies at high risk of bias
[7] Sadineni 2017 reported low volume of contrast agent <100ml
[8] Ferrario 2008 reported high volume of contrast agent >140 ml; Sadineni 2017 reported high volume of contrast agent ≥100 ml

Other outcomes: Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.9%**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
Mortality: all-cause mortality (30 days)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/102 (0%)	3/103 (2.9%)	RR 0.14 (0.01 to 2.76)	3 fewer per 100 (from 3 fewer to 5 more)	VERY LOW
Mortality: all-cause mortality (30 days - 1 year)											
2	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	48/1340 (3.6%)	35/1347 (2.6%)	RR 1.38 (0.9 to 2.12)	1 more per 100 (from 0 fewer to 3 more)	MODERATE
In-hospital mortality											
1	randomised trials[6]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/77 (6.5%)	2/79 (2.5%)	RR 2.56 (0.51 to 12.83)	4 more per 100 (from 1 fewer to 30 more)	VERY LOW
								0%		-	
Need for renal replacement therapy: dialysis											
6	randomised trials[7]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	21/2769 (0.76%)	25/2731 (0.92%)	RR 0.83 (0.48 to 1.46)	0 fewer per 100 (from 0 fewer to 0 more)	LOW
Adverse events											

4	randomised trials[8]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	111/2492 (4.5%)	114/2415 (4.7%)	RR 0.94 (0.73 to 1.22)	0 fewer per 100 (from 1 fewer to 1 more)	MODERATE
Hospital length of stay in days (Better indicated by lower values)											
1	randomised trials[9]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	102	98	-	MD 0.50 lower (0.93 to 0.07 lower)	HIGH

[1] Ertuk 2014
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Ertuk 2014 (1 year); Weisbord 2018 (3 months)
[5] 95% confidence interval crosses one end of a defined MID interval
[6] Gomes 2005
[7] ACT investigators 2011; Ertuk 2014; Gomes 2005; Reinecke 2007; Sadineni 2017; Weisbord 2018
[8] ACT investigators 2011 (any adverse events or any serious adverse events [stroke, myocardial infarction, pneumonia, sepsis and acute pulmonary edema]); Fung 2004 (clinical heart failure so patients could not complete sodium chloride infusion regimen); Kay 2003 (congestive heart failure, uncomplicated non-ST-segment elevation mycardial infarction, nausea)
[9] Kay 2003

Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium chloride 0.9%**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
13	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	326/3128 (10.4%)	326/3100 (10.5%)	RR 0.99 (0.85 to 1.14)	0 fewer per 100 (from 2 fewer to 1 more)	HIGH

[1] ACT investigators 2011; Albabtain 2013; Baskurt 2009; Castini 2010; Erturk 2014; Ferrario 2009; Fung 2004; Gomes 2005; Hafiz 2012; Kay 2003; Khalili 2006; Saitoh 2011; Weisbord 2018

Oral NAC + sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
4	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	129/1525 (8.5%)	145/1534 (9.5%)	RR 0.89 (0.71 to 1.12)	1 fewer per 100 (from 3 fewer to 1 more)	MODERATE

[1] Castini 2010; Chong 2015; Hafiz 2012; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Oral NAC + sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Sodium bicarbonate	Relative (95% CI)	Absolute	
Mortality: all-cause mortality (30 days)											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/153 (0.65%)	0/157 (0%)	RR 3.08 (0.13 to 74.98)	-	VERY LOW
Mortality: all-cause mortality (90 days)											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	40/1238 (3.2%)	33/1254 (2.6%)	RR 1.23 (0.78 to 1.93)	1 more per 100 (from 1 fewer to 2 more)	LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	14/1238 (1.1%)	16/1254 (1.3%)	RR 0.89 (0.43 to 1.81)	0 fewer per 100 (from 1 fewer to 1 more)	LOW

[1] Chong 2015
[2] >33.3% of weighted data from studies at high risk of bias

[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Weisbord 2018

Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.9% vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
3	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	119/1372 (8.7%)	126/1385 (9.1%)	RR 0.95 (0.75 to 1.21)	0 fewer per 100 (from 2 fewer to 2 more)	MODERATE

[1] Castini 2010; Hafiz 2012; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Oral NAC + sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
6	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	166/2020 (8.2%)	207/2036 (10.2%)	RR 0.81 (0.67 to 0.98)	2 fewer per 100 (from 0 fewer to 3 fewer)	LOW

[1] Briguori 2007; Chong 2015; Hafiz 2012; Lee 2011; Maioli 2008; Weisbord 2018
[2] i-squared >33.3%
[3] 95% confidence interval crosses one end of a defined MID interval

Subgroup analyses (outcome: CI-AKI): Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Oral NAC + sodium bicarbonate	Relative (95% CI)	Absolute	
Subgroup: diabetes											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/59 (20.3%)	8/62 (12.9%)	RR 1.58 (0.69 to 3.58)	7 more per 100 (from 4 fewer to 33 more)	LOW
Subgroup: low volume of contrast agent											
1	randomised trials[3]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	2/137 (1.5%)	8/134 (6%)	RR 0.24 (0.05 to 1.13)	45 fewer per 1000 (from 57 fewer to 8 more)	MODERATE
Subgroup: high volume of contrast agent											
2	randomised trials[5]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/135 (13.3%)	16/131 (12.2%)	RR 1.11 (0.59 to 2.09)	1 more per 100 (from 5 fewer to 13 more)	LOW

[1] Maioli 2008
[2] 95% confidence interval crosses both ends of a defined MID interval
[3] Lee 2011 did not provide a definition of low volume of contrast agent
[4] 95% confidence interval crosses one end of a defined MID interval
[5] Lee 2011 reported high volume of contrast agent ≥140 mL and >5 times body weight (kg) per serum creatinine (ml/dl); Maioli 2008 reported high volume of contrast agent >140ml

Other outcomes: Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Oral NAC + sodium bicarbonate	Relative (95% CI)	Absolute	
Mortality: all-cause mortality (30 days)											
2	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/342 (0.29%)	3/349 (0.86%)	RR 0.44 (0.06 to 2.94)	0 fewer per 100 (from 1 fewer to 2 more)	VERY LOW
Mortality - All-cause mortality (30 days-6 months)											
3	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	45/1679 (2.7%)	36/1700 (2.1%)	RR 1.27 (0.82 to 1.95)	1 more per 100 (from 0 fewer to 2 more)	MODERATE
Need for renal replacement therapy: dialysis											
1	randomised trials[6]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	14/1238 (1.1%)	16/1257 (1.3%)	RR 0.89 (0.44 to 1.81)	0 fewer per 100 (from 1 fewer to 1 more)	LOW

[1] Chong 2015; Lee 2011
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Lee 2011 (30 days - 6 months); Maioli 2008 (follow-up time for mortality not reported); Weisbord 2018 (3 months)
[5] 95% confidence interval crosses one end of a defined MID interval
[6] Weisbord 2018

Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium chloride 0.9% vs oral NAC + sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	Oral NAC + sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
5	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	156/1867 (8.4%)	191/1885 (10.1%)	RR 0.83 (0.67 to 1.01)	2 fewer per 100 (from 3 fewer to 0 more)	LOW

[1] Briguori 2007; Hafiz 2012; Lee 2011; Maioli 2008; Weisbord 2018
[2] i-squared >33.3%
[3] 95% confidence interval crosses one end of a defined MID interval

Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	IV NAC + sodium chloride 0.9%	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/102 (13.7%)	13/102 (12.7%)	RR 1.08 (0.53 to 2.18)	1 more per 100 (from 6 fewer to 15 more)	VERY LOW

[1] Erturk 2014
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: Oral NAC + sodium chloride 0.9% vs IV NAC + sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral NAC + sodium chloride 0.9%	IV NAC + sodium chloride 0.9%	Relative (95% CI)	Absolute	
Mortality: all-cause mortality (30 days)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/102 (0%)	1/102 (0.98%)	RR 0.33 (0.01 to 8.09)	1 fewer per 100 (from 1 fewer to 7 more)	VERY LOW
Mortality: all-cause mortality (1 year)											

1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/102 (7.8%)	12/102 (11.8%)	RR 0.67 (0.28 to 1.56)	4 fewer per 100 (from 8 fewer to 7 more)	VERY LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/102 (0.98%)	0/102 (0%)	RR 3 (0.12 to 72.79)	-	VERY LOW

[1] Ertuk 2014
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

Oral NAC + sodium bicarbonate vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium bicarbonate**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
2	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	134/1337 (10%)	115/1324 (8.7%)	RR 1.15 (0.91 to 1.45)	1 more per 100 (from 1 fewer to 4 more)	MODERATE

[1] Hafiz 2012; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Oral NAC + sodium bicarbonate vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium bicarbonate**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	

Mortality: all-cause mortality (90 days)											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/1257 (2.1%)	28/1244 (2.3%)	RR 0.95 (0.57 to 1.61)	0 fewer per 100 (from 1 fewer to 1 more)	LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	16/1257 (1.3%)	15/1244 (1.2%)	RR 1.06 (0.52 to 2.13)	0 more per 100 (from 1 fewer to 1 more)	LOW

[1] Weisbord 2018
[2] 95% confidence interval crosses both ends of a defined MID interval

Oral NAC + sodium bicarbonate vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium bicarbonate**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
5	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	151/1566 (9.6%)	140/1564 (9%)	RR 1.08 (0.86 to 1.34)	1 more per 100 (from 1 fewer to 3 more)	MODERATE

[1] Caglar 2014; Chong 2015; Hafiz 2012; Heng 2008; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

Other outcomes: Oral NAC + sodium bicarbonate vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium bicarbonate**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	

Mortality: all-cause mortality (30 days)											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/156 (1.3%)	0/157 (0%)	RR 5.03 (0.24 to 103.97)	-	VERY LOW
Mortality: all-cause mortality (90 days)											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	27/1257 (2.1%)	33/1254 (2.6%)	RR 0.82 (0.49 to 1.35)	0 fewer per 100 (from 1 fewer to 1 more)	LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	16/1257 (1.3%)	16/1254 (1.3%)	RR 1 (0.5 to 1.99)	0 fewer per 100 (from 1 fewer to 1 more)	LOW
Adverse events											
1	randomised trials[5]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/28 (3.6%)	0/32 (0%)	RR 3.41 (0.14 to 80.59)	-	VERY LOW

[1] Chong 2015
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Weisbord 2018
[5] Heng 2008 (congestive heart failure)

Sensitivity analysis excluding studies with a high risk of bias: Oral NAC + sodium bicarbonate vs sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral NAC + sodium bicarbonate**	**Sodium bicarbonate**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
3	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	134/1387 (9.7%)	119/1383 (8.6%)	RR 1.12 (0.89 to 1.42)	1 more per 100 (from 1 fewer to 4 more)	MODERATE

[1] Caglar 2014; Hafiz 2012; Weisbord 2018
[2] 95% confidence interval crosses one end of a defined MID interval

IV NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.45%	Sodium chloride 0.45%	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
3	randomised trials[1]	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	15/190 (7.9%)	28/194 (14.4%)	RR 0.46 (0.16 to 1.36)	8 fewer per 100 (from 12 fewer to 5 more)	VERY LOW

[1] Carbonell 2007; Carbonell 2010; Poletti 2007
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] i-squared >33.3%
[4] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: IV NAC + sodium chloride 0.45% vs sodium chloride 0.45%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.45%	Sodium chloride 0.45%	Relative (95% CI)	Absolute	
Mortality: all-cause mortality (1 year)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/39 (15.4%)	9/42 (21.4%)	RR 0.72 (0.28 to 1.83)	6 fewer per 100 (from 15 fewer to 18 more)	VERY LOW
Mortality: in-hospital mortality											

2	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/146 (4.8%)	12/151 (7.9%)	RR 0.61 (0.25 to 1.5)	3 fewer per 100 (from 6 fewer to 4 more)	VERY LOW
Need for renal replacement therapy: dialysis											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/39 (0%)	1/42 (2.4%)	RR 0.36 (0.02 to 8.54)	2 fewer per 100 (from 2 fewer to 18 more)	VERY LOW

[1] Carbonell 2010 (chronic renal disease arm)
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Carbonell 2007 (normal renal function arm); Carbonell 2010 (chronic renal disease arm)

IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV NAC + sodium chloride 0.9%**	**Sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
10	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	129/975 (13.2%)	122/940 (13%)	RR 1.05 (0.84 to 1.32)	1 more per 100 (from 2 fewer to 4 more)	LOW

[1] Erturk 2014; Jaffery 2012; Kama 2014; Koc 2012; Kotlyar 2005; Rashid 2004; Traub 2013; Turedi 2016; Webb 2004
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Subgroup analyses (outcome: CI-AKI): IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.9%	Sodium chloride 0.9%	Relative (95% CI)	Absolute	
Subgroup: chronic kidney disease											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/57 (10.5%)	6/41 (14.6%)	RR 0.72 (0.25 to 2.07)	4 fewer per 100 (from 11 fewer to 16 more)	LOW
Subgroup: diabetes											
1	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/80 (2.5%)	3/80 (3.8%)	RR 0.67 (0.11 to 3.88)	1 fewer per 100 (from 3 fewer to 11 more)	VERY LOW
Subgroup: older people >75 years											
1	randomised trials[5]	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/80 (0%)	6/80 (7.5%)	RR 0.08 (0 to 1.34)	7 fewer per 100 (from 8 fewer to 3 more)	VERY LOW
Subgroup: high volume of contrast agent											
2	randomised trials[6]	serious[4]	serious[7]	no serious indirectness	serious[2]	none	5/98 (5.1%)	10/89 (11.2%)	RR 0.5 (0.08 to 3.18)	56 fewer per 1000 (from 103 fewer to 245 more)	VERY LOW

[1] Jaffery 2012
[2] 95% confidence interval crosses both ends of a defined MID interval
[3] Koc 2012
[4] >33.3% of weighted data from studies at moderate or high risk of bias
[5] Koc 2012 reported older people ≥70 years
[6] Jaffery 2012 reported high volume of contrast agent >300 ml; Koc 2012 reported high volume of contrast agent >100ml
[7] I-Squared >33.3%

Other outcomes: IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.9%	Sodium chloride 0.9%	Relative (95% CI)	Absolute	

Mortality: all-cause mortality (up to 8 days)											
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/220 (3.2%)	5/227 (2.2%)	RR 1.44 (0.47 to 4.48)	1 more per 100 (from 1 fewer to 8 more)	VERY LOW
Mortality: all-cause mortality (up to 30 days)											
3	randomised trials[4]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/528 (1.3%)	10/522 (1.9%)	RR 0.69 (0.27 to 1.81)	1 fewer per 100 (from 1 fewer to 2 more)	VERY LOW
Mortality: all-cause mortality (1 year)											
1	randomised trials[5]	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/102 (11.8%)	7/103 (6.8%)	RR 1.73 (0.71 to 4.22)	5 more per 100 (from 2 fewer to 22 more)	VERY LOW
Mortality: in-hospital mortality											
2	randomised trials[7]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	12/291 (4.1%)	13/279 (4.7%)	RR 0.94 (0.45 to 1.96)	0 fewer per 100 (from 3 fewer to 4 more)	LOW
Need for renal replacement therapy											
3	randomised trials[8]	no serious risk of bias	serious[9]	no serious indirectness	very serious[3]	none	11/223 (4.9%)	17/225 (7.6%)	RR 0.68 (0.34 to 1.36)	2 fewer per 100 (from 5 fewer to 3 more)	VERY LOW
Length of hospital stay in days (Better indicated by lower values)											
1	randomised trials[10]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	192	206	-	MD 0.40 lower (0.98 lower to 0.18 higher)	MODERATE

[1] Webb 2014
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Ertuk 2014 (30 days); Jaffrey 2012 (30 days); Webb 2014 (>8 days)
[5] Ertuk 2014
[6] >33.3% of weighted data from studies at moderate or high risk of bias
[7] Jaffrey 2012; Turedi 2016
[8] Ertuk 2014 (dialysis); Kama 2014 (renal replacement therapy due to CI-AKI); Turedi 2016 (hemodialysis or peritonael dialysis requirement for severe renal failure)
[9] i-squared >33.3%

[10] Jaffery 2012
[11] 95% confidence interval crosses one end of a defined MID interval

Sensitivity analysis excluding studies with a high risk of bias: IV NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.9%	Sodium chloride 0.9%	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
8	randomised trials[1]	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	92/781 (11.8%)	88/736 (12%)	RR 1.02 (0.78 to 1.33)	0 more per 100 (from 3 fewer to 4 more)	VERY LOW

[1] Erturk 2014; Jaffery 2012; Kama 2014; Koc 2012; Kotlyar 2005; Rashid 2004; Traub 2013; Turedi 2016
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] i-squared >33.3%
[4] 95% confidence interval crosses both ends of a defined MID interval

IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.9%	Sodium chloride 0.9% + sodium bicarbonate	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
2	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/121 (22.3%)	22/121 (18.2%)	RR 1.23 (0.74 to 2.03)	4 more per 100 (from 5 fewer to 19 more)	LOW

[1] Kama 2014; Turedi 2016
[2] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: IV NAC + sodium chloride 0.9% vs sodium chloride 0.9% + sodium bicarbonate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC + sodium chloride 0.9%	Sodium chloride 0.9% + sodium bicarbonate	Relative (95% CI)	Absolute	
Mortality: in-hospital mortality											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/85 (12.9%)	10/85 (11.8%)	RR 1.1 (0.49 to 2.45)	1 more per 100 (from 6 fewer to 17 more)	LOW
Need for renal replacement therapy											
2	randomised trials[3]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/121 (9.1%)	11/121 (9.1%)	RR 1 (0.45 to 2.22)	0 fewer per 1000 (from 50 fewer to 111 more)	LOW
								8.1%		0 fewer per 1000 (from 45 fewer to 99 more)	

[1] Turedi 2016
[2] 95% confidence interval crosses both ends of a defined MID interval
[3] Kama 2014 (renal replacement therapy due to CI-AKI); Turedi 2016 (hemodialysis or peritonael dialysis requirement for severe renal failure)

IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV NAC bolus + oral NAC	Control	Relative (95% CI)	Absolute	
CI-AKI (as reported by study)											
2	randomised trials[1]	very serious[2]	very serious[3]	no serious indirectness	very serious[4]	none	54/341 (15.8%)	62/218 (28.4%)	RR 0.61 (0.21 to 1.83)	11 fewer per 100 (from 22 fewer to 24 more)	VERY LOW

[1] Aslanger 2012; Marenzi 2006
[2] >33.3% of weighted data from studies at high risk of bias
[3] No explanation was provided
[4] 95% confidence interval crosses both ends of a defined MID interval

Other outcomes: IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV NAC bolus + oral NAC + IV sodium chloride 0.9%**	**IV sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
Mortality: in-hospital mortality											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/233 (3.4%)	13/119 (10.9%)	RR 0.31 (0.13 to 0.74)	8 fewer per 100 (from 3 fewer to 10 fewer)	MODERATE
Need for renal replacement therapy											
1	randomised trials[3]	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	3/189 (1.6%)	6/119 (5%)	RR 0.31 (0.08 to 1.23)	3 fewer per 100 (from 5 fewer to 1 more)	LOW

[1] Marenzi 2006
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] Marenzi 2006 (acute renal failure requiring renal replacement therapy)
[4] 95% confidence interval crosses one end of a defined MID interval

Sensitivity analysis excluding studies with a high risk of bias: IV NAC bolus + oral NAC + sodium chloride 0.9% vs sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV NAC bolus + oral NAC + IV sodium chloride 0.9%**	**IV sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	

CI-AKI (as reported by study)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/233 (11.6%)	39/119 (32.8%)	RR 0.35 (0.23 to 0.55)	21 fewer per 100 (from 15 fewer to 25 fewer)	MODERATE

[1] Marenzi 2006
[2] >33.3% of weighted data from studies at moderate or high risk of bias

IV NAC (bolus) + IV sodium chloride 0.9% vs IV sodium chloride 0.9%

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV NAC (bolus) + IV sodium chloride 0.9%**	**IV sodium chloride 0.9%**	**Relative (95% CI)**	**Absolute**	
CI-AKI (as reported by study)											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18/126 (14.3%)	25/123 (20.3%)	RR 0.70 (0.4 to 1.22)	6 fewer per 100 (from 12 fewer to 4 more)	MODERATE

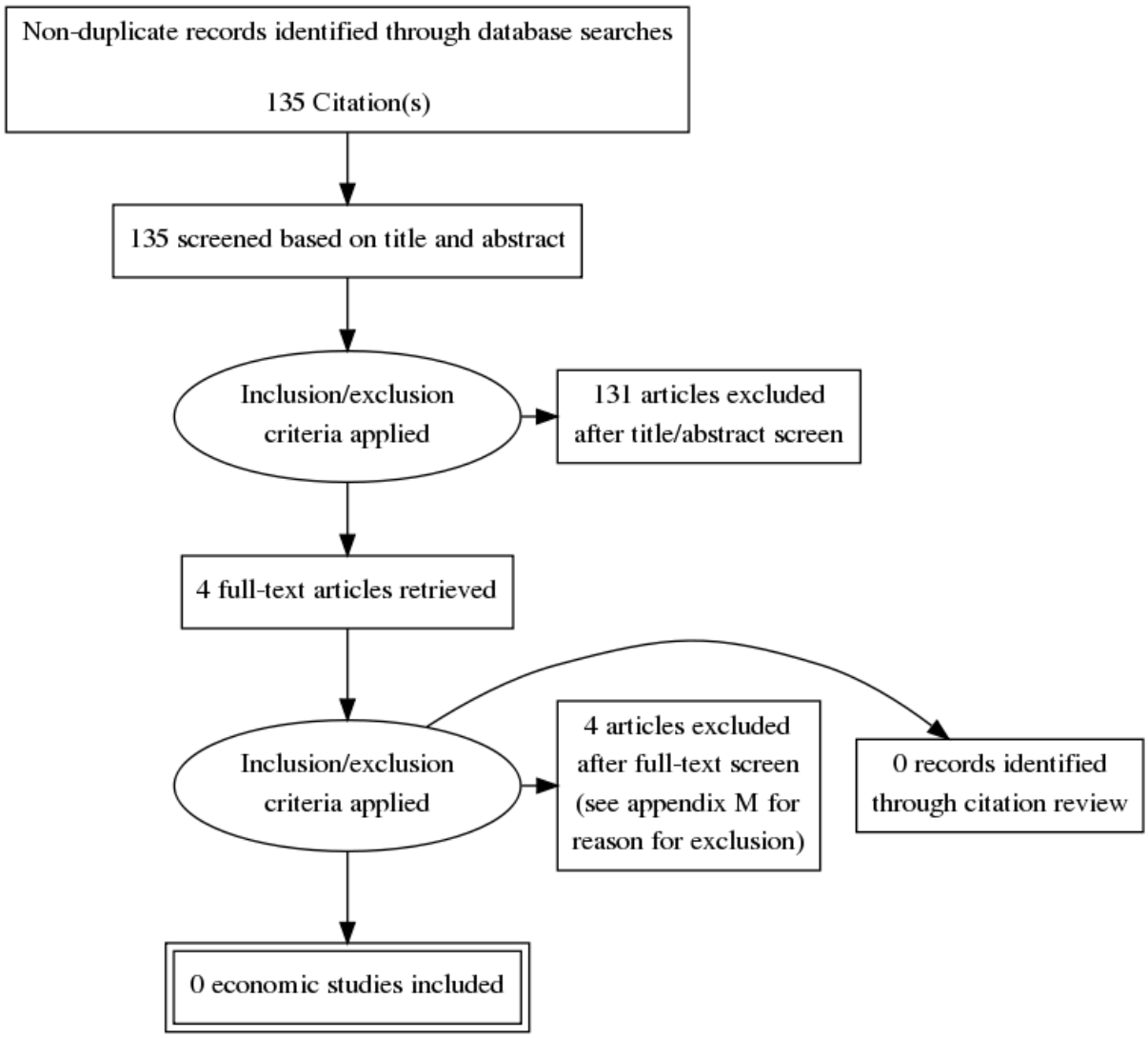
[1] Thiele 2010
[2] 95% confidence interval crosses one end of a defined MID interval

Network meta-analyses

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CI-AKI								
70	RCT	21,825	See appendix G	Serious[1]	Not serious	Serious[2]	No serious	Low

1. >33.3% of studies in the NMA at moderate or high risk of bias
2. DIC for a random-effects model lower than the DIC for a fixed-effects model

Appendix I – Economic evidence study selection



Appendix J – Economic evidence tables

None – no economic evaluations relevant to the review question were found.

Appendix K – Health economic evidence profiles

None – no economic evaluations relevant to the review question were found.

Appendix L – Health economic analysis

Introduction

We did not find any relevant published cost–utility analyses; therefore, we undertook health economic modelling to answer the review question in Table 13. The developers of the previous iteration of the guideline (CG169) created a model to answer this question. After discussion with the committee, we agreed to adapt this existing model as it was deemed to be suitable for decision-making.

Table 13: Research question addressed by economic model

Research question	What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?

Methods

Model overview

Modelled population(s), intervention(s), comparator(s) and outcome(s)

In the previous iteration of the model, the base-case population was chronic kidney disease (CKD) stage 3–4. The committee was happy that CKD was a good representation of a population 'at risk' of CI-AKI to answer the review question. After reviewing the natural history data available to us relating to CKD progression, mortality and the probability of end-stage renal disease and death following CI-AKI, we adapted the original population slightly to also incorporate those patients who had pre-dialysis stage 5 CKD. This was because much of the published data are reported in terms of progression to renal replacement therapy (RRT; a sub-set of stage 5) rather than progression to CKD stage 5 as a whole. A portion of people with stage 5 CKD may be classed as 'pre-dialysis'; these people are now included in the initial state and can progress to RRT, as can people in stages 3 and 4.

In alignment with the previous model, we used percutaneous coronary intervention (PCI) as a proxy for the probability of repeat scans, as this is a common procedure in which people with CKD are likely to receive iodine based contrast media. The interventions and comparators were determined by the randomised controlled trials (RCTs) included in the clinical review. Quality-adjusted life-years (QALYs) were derived using NICE's preferred methods. Table 14 summarises the modelled population, interventions, comparators and outcomes.

Table 14: Economic Model PICO

Population	Adults who are at risk (defined as CKD stages 3, 4 and pre-dialysis stage 5) of CI-AKI
Intervention	1. No (IV) hydration 2. NAC (IV bolus & oral) + sodium chloride 0.9% (IV) 3. NAC (IV bolus) + sodium chloride 0.9% (IV) 4. NAC (IV) + sodium chloride 0.45% (IV) 5. NAC (IV) + sodium chloride 0.9% (IV) 6. NAC (oral) 7. NAC (oral) + sodium bicarbonate (IV)

	8. NAC (oral) + sodium chloride 0.45% (IV) 9. NAC (oral) + sodium chloride 0.9% (IV) 10. Oral fluids 11. Sodium bicarbonate (IV) 12. Sodium bicarbonate (oral) + oral fluids 13. Sodium chloride 0.45% (IV) 14. Sodium chloride 0.45% (IV) + sodium bicarbonate (IV) 15. Sodium chloride 0.9% (IV) 16. Sodium chloride 0.9% (IV) + sodium bicarbonate (IV) 17. Sodium citrate (oral)
Comparator	18. Each other
Outcomes	• Rates of CI-AKI • Life-years • Mortality • AKI-induced ESRD • Progression to RRT • Costs • QALYs

CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; IV, intravenous; NAC, N-acetylcysteine; QALY, quality-adjusted life-year; RRT, renal replacement therapy.

Type of evaluation, time horizon, perspective, discount rate

As per the NICE Reference Case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS, which assesses costs and health benefits using a lifetime horizon, and uses a discount rate of 3.5% per annum for both costs and health benefits.

Model structure

In agreement with the committee, we adapted the model structure from the previous guideline. The model uses a Markov structure with states based on CKD stage or CI-AKI. The committee agreed that a three-month cycle length is appropriate to capture relevant events and changes between states. Figure 5 illustrates the model structure.

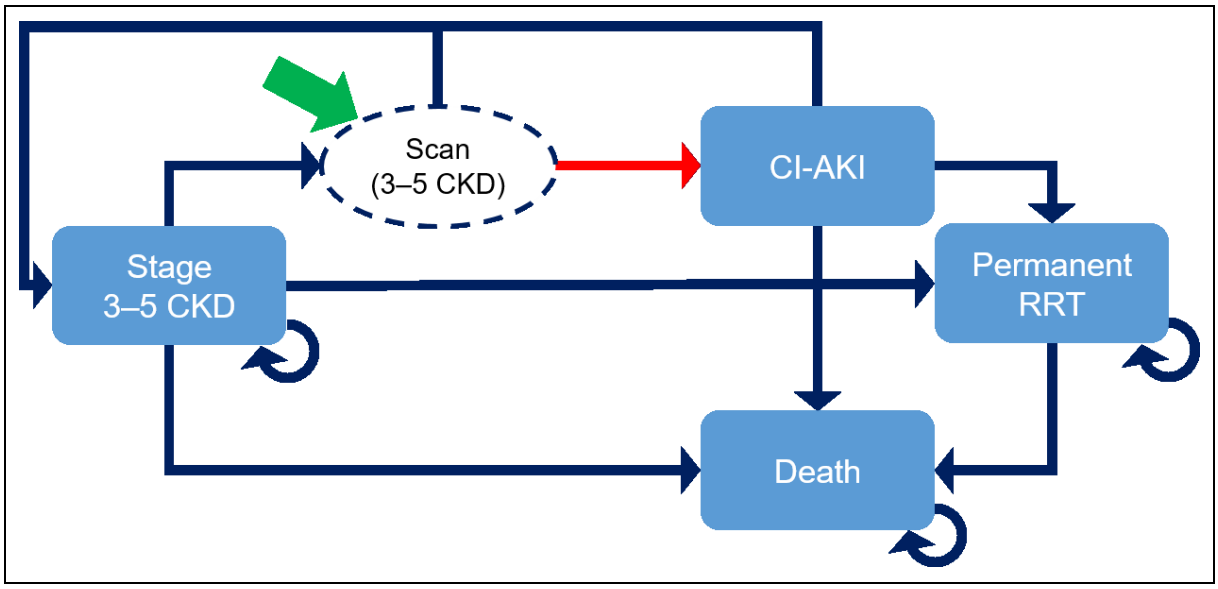


Figure 5: Model structure

There are 4 health states within the model (blue boxes): stage 3–5 CKD (pre-dialysis), CI-AKI, permanent RRT and death (see Table 15 for a summary of these health states). At model initiation, all people are in stage 3–5 CKD (pre-dialysis) and start by undergoing a scan, represented by the green arrow in Figure 5. As a result of this scan they can either develop CI-AKI and move to the corresponding state, or they are assumed to have no complications and return to the 'Stage 3–5 CKD' state. The risk of CI-AKI following a scan (indicted by red arrow) is a key model parameter; it is obtained from the network meta-analysis (NMA) undertaken as part of the clinical review and represents the relative effectiveness of each of the interventions in terms of risk of CI-AKI. People who develop CI-AKI following a scan can either return to the 'Stage 3–5 CKD' state (assuming complete resolution of CI-AKI), require permanent RRT as a result of their CI-AKI, or die within the cycle (the CI-AKI increases this risk). Those people who return to the 'Stage 3–5 CKD' state following a scan or an episode of CI-AKI may need repeat scans, which have the same potential consequences as the first scan, or they may progress to permanent RRT.

People who are in the permanent RRT state can either be on dialysis or receive a kidney transplant (note that the possibility of transplantation was not included in the previous iteration of the model). Simulated people stay in this state until they die and are assumed not to have repeat contrast-enhanced scans. The committee advised that some people on dialysis may undergo scans using contrast; however, this would be avoided where possible and therefore this simplifying assumption was acceptable for decision making purposes. CI-AKI in renal transplant patients is not within the scope of the update; therefore, we assumed that anyone who has a transplant will not undergo repeat contrast-enhanced scans.

Table 15: Modelled health states

Health state	Summary
Stage 3–5 CKD (pre-dialysis)	Includes people with stage 3, stage 4, and stage 5 (pre-dialysis) CKD. People initially enter this state following a scan if they don't experience CI-AKI or if they recover fully from an episode of CI-AKI. People can remain in this state if they don't have another scan. They are at risk of repeat scans (with the associated risk of CI-AKI), natural progression to permanent RRT or death.
CI-AKI	A proportion of people in the stage 3–5 CKD state will enter this state each cycle if they have a repeat scan and experience CI-AKI. They spend one cycle here only, then can move to any of the other states.
Permanent RRT	Includes people who have received a transplant and people on dialysis. People enter this state if they have naturally progressed from a lower severity of CKD, or if an episode of CI-AKI has led to the requirement for permanent RRT. People remain in this state until they die.
Death	People can transition to the death health state from any of the other three states. They remain here for the duration of the model.

CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy.

Each of the health states (apart from death) is associated with costs and QALYs, which accumulate over the model horizon. A half-cycle correction is applied to account for the fact that people may transition from one state to another at any point throughout a cycle, rather than only at the start.

Model parameterisation

Identifying sources of parameters

With the exception of treatment effects, which were comprehensively updated (see below), we used the parameters from the previous iteration of the model unless we could find anything more appropriate or recent from informal searches. These informal searches aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed) and GoogleScholar. Where we could not identify suitable evidence from informal searches or it was not present/appropriate in the existing model, sources for parameters were also sought from the guideline committee directly. Any key parameters that were different to the previous iteration of the model were validated by the committee.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, we prefer more powerful studies (based on sample size and/or number of events).

- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

Parameters

Key calculations and parameters are summarised here. Please see the full table of parameters (Table 33) for a complete summary of all parameters used in the model, including their distributions and sources.

Cohort parameters and natural history

Initial cohort settings

The base-case cohort has stage 3–5 CKD (pre-dialysis) to represent a population who are 'at risk' of CI-AKI. The cohort is 50% male and is aged 70 years in line with the previous iteration of the model.

Natural progression to permanent RRT

The previous iteration of the model used a Norwegian study to obtain the probability of progressing from stages 3–4 CKD to stage 5 CKD (Eriksen & Ingebretsen, 2006). This study has two main limitations: firstly, it is from a non-UK population and, secondly, it only includes people with stage 3 CKD at baseline (therefore, it may underestimate rates of progression). We were able to find a UK study that allowed us to obtain the probability of progressing from stages 3–5 CKD to RRT (Marks et al., 2012). This large, UK study included 3,414 patients with CKD stages 3–5 who were not on RRT at baseline. The study reports rates of RRT initiation after 6 years of follow-up, allowing us to calculate the 3-month probability of transitioning to the permanent RRT state (Table 16). In the 2 oldest age categories (age 85–94 years, and 95–104 years) there were no events within the study; therefore, we used linear extrapolation based on observed rates (on the log scale) in the younger age groups to obtain predicted rates in the older two age groups. At base-case values, the regression equation is: $\ln(rate) = -0.91 - 0.05age$.

Table 16: Progression from stages 3–5 CKD to RRT (Marks et al., 2012)

Age group	Rate of progression per patient-year of follow-up	3-month probability of progression
15–24 years	0.143	3.52%
25–34 years	0.077	1.91%
35–44 years	0.063	1.56%
45–54 years	0.044	1.10%
55–64 years	0.022	0.54%
65–74 years	0.015	0.36%
75–84 years	0.0065	0.16%
85–94 years	0.0049[a]	0.12%
95–104 years	0.0030[a]	0.08%

(a) Obtained from linear extrapolation of rates (on log scale) in younger age groups.
CKD, chronic kidney disease; RRT, renal replacement therapy.

Mortality in stages 3–5 CKD

We used the Norwegian study by Eriksen and Ingebretsen (2006) for mortality in stages 3–5 CKD, as we were unable to find evidence from the UK that reported data in a form suitable for use within the model. All included participants within the study had stage 3 CKD at baseline so did not exactly match our modelled population of stages 3–5 CKD, and therefore mortality rates may be underestimated. The study reports data as standardised mortality ratios (SMRs) relative to the general population (Table 17). Our model applies these SMRs to National Life Table data for England and Wales (Office for National Statistics, 2018) to obtain age-specific probabilities of death in stages 3–5 CKD.

Table 17: Standardised mortality ratios versus the general population in stages 3–5 CKD (Eriksen & Ingebretsen, 2006)

Age group	SMR in Men	SMR in Women
<69 years	3.6	2.7
70–79 years	2.4	1.8
>79 years	2.3	2.1

CKD, chronic kidney disease; SMR, standardised mortality ratio.

Mortality in RRT

The previous model used a French study to obtain standardised mortality ratios versus the general population in people on dialysis (Villar et al., 2007). Following advice from the committee, we updated the model to include people who have received kidney transplants within the permanent RRT state. Therefore, we wanted mortality data to reflect this. The UK Renal Registry (UK Renal Registry, 2018) provided us with the relative risk of death in people receiving RRT compared with the general population in the 2016 registry cohort (Table 18), which we applied to UK Life Table data (ONS) to obtain the probability of death in the permanent RRT state by age. The Renal Registry reports a relative risk of 1.5 in the 85+ years age group; however, when applied to life table data, this resulted in people in the RRT state having a lower probability of death than those in the CKD 3–5 state, which lacked face-validity. We note that Renal Registry data for other years do not feature a drop-off in risk of the same magnitude, which further suggests that this finding is artefactual. We therefore made an assumption that the relative risk in the 85+ years group was the same as the 80–84 years group.

Table 18: Relative risk of death compared with the UK general population in prevalent renal replacement therapy patients (UK Renal Registry, 2018)

Age group	Relative risk of death (2016 cohort)
Age 20–24 years	24.7
Age 25–29 years	23.0
Age 30–34 years	21.0
Age 35–39 years	21.2
Age 40–44 years	16.6
Age 45–49 years	15.8
Age 50–54 years	12.7
Age 55–59 years	11.4
Age 60–64 years	9.7
Age 65–69 years	8.9
Age 70–74 years	7.8
Age 75–79 years	5.9
Age 80–84 years	4.9
Age 85+ years	4.9[a]

(a) Assumed to have the same relative risk as the 80–84 years age group.

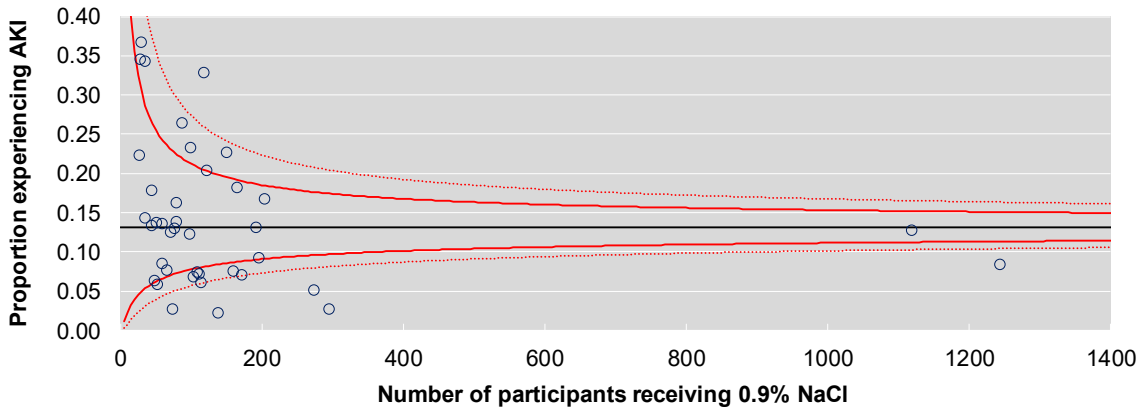
Baseline risk of CI-AKI

We explored a number of different sources for the baseline risk of CI-AKI. The base-case rate was obtained from an Italian study of 502 people with CKD (Maioli et al., 2008). We used this as the base case because it was European, the population was appropriate for our modelled cohort (CKD) and it was very similar to the study we used to obtain mortality data (same centre, investigators and interventions). In this study, 29 out of a total of 252 people (11.5%) developed CI-AKI in the sodium chloride 0.9% + NAC arm.

We explored the impact of using estimates from other individual studies in sensitivity analysis. The only UK study that was included in the clinical review (Rashid et al., 2004) included a small subset of people (n=21) who had raised serum creatinine. Of these, 3 (14.3%) experienced CI-AKI in the sodium chloride 0.9% arm. We also explored the 3 different rates that were used in the previous iteration of the model: a low rate of 2.2% (Mueller et al., 2002), a medium rate of 19.2% (Dangas et al., 2005) and a high rate of 30.0% (Mehran et al., 2004).

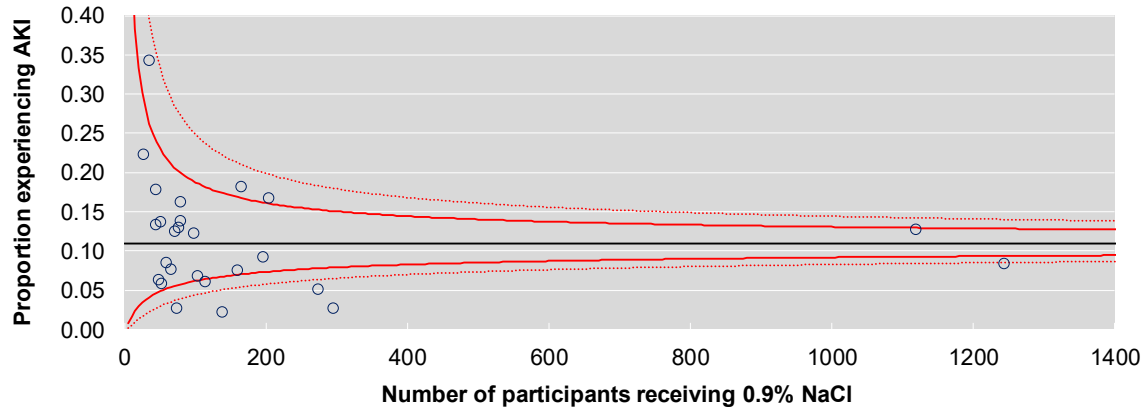
We noted that baseline rates of CI-AKI differed substantially between the studies; for example, in the sodium chloride 0.9% study arms the rate varied from 2.2% (Mueller et al., 2002) to 36.7% (Sadineni et al., 2017). In an attempt to account for this, we conducted a supplementary analysis in which we synthesised the rates across all sodium chloride 0.9% study arms. This interventional arm was chosen for the baseline synthesis because it had the greatest amount of data available. The rate of CI-AKI from this pooled analysis was 13.1%, which was in reasonably close alignment with the rates from the Maioli et al., (2008) and Rashid et al., (2004) studies discussed above. To better understand the variation in rates of CI-AKI between trials, we stratified the studies with sodium chloride 0.9% arms into elective and emergency and conducted separate pooled analyses, as we would expect emergency patients to have higher overall morbidity and therefore be at an overall higher risk of CI-AKI. The pooled rates of CI-AKI were 10.8% in elective settings and 19.6% in emergency settings. Funnel plots showing the rates of CI-AKI in 0.9% sodium chloride arms against the number

of participants in the study are shown for the base case (Figure 6), the elective population (Figure 7) and the emergency population (Figure 8). These funnel plots show the risk of CI-AKI against the number of participants in each study who received sodium chloride 0.9%. The plots display the increasing precision in the estimate as the study size increases. They show that most of the observed variability in event-rates is to be expected, given the imprecision inherent in small sample sizes: relatively few of the estimates lie outside the expected uncertainty intervals.



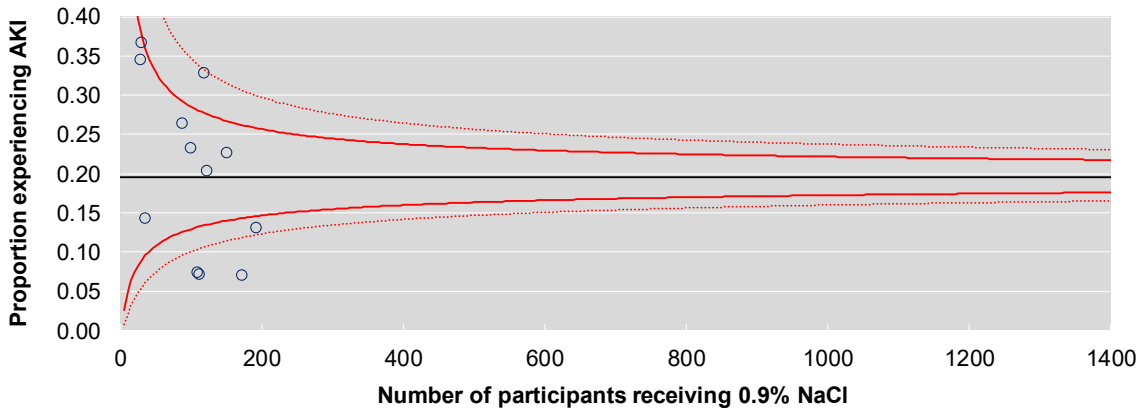
AKI, acute kidney injury; NaCl, sodium chloride.

Figure 6: Funnel plot, rates of CI-AKI in 0.9% sodium chloride arms, base case



AKI, acute kidney injury; NaCl, sodium chloride.

Figure 7: Funnel plot, rates of CI-AKI in 0.9% sodium chloride arms, elective studies



AKI, acute kidney injury; NaCl, sodium chloride.

Figure 8: Funnel plot, rates of CI-AKI in 0.9% sodium chloride arms, emergency studies

Table 19 summarises the different baseline rates of CI-AKI; we explore how varying the baseline rate of CI-AKI affects results in sensitivity analyses.

Table 19: Baseline risk of CI-AKI

Source	Incidence (%), 95% CI
Maioli et al. 2008[a]	11.5 (7.9, 15.7)
Rashid et al. 2004[b]	14.3 (3.2, 31.7)
Pooled RCT data, all trials[b]	13.1 (12.2, 14.0)
Pooled RCT data, elective trials[b]	10.8 (9.9, 11.7)
Pooled RCT data, emergency trials[b]	19.6 (10.6, 33.4)
Mueller et al. 2002[b]	2.2 (0.5, 5.2)
Dangas et al. 2005[c]	19.2 (17.5, 21.0)
Mehran et al. 2004[c]	30.0 (27.7, 32.4)

(a) Baseline intervention is sodium chloride 0.9% + N-acetylcysteine.
(b) Baseline intervention is sodium chloride 0.9%.
(c) Baseline intervention is sodium chloride 0.45%.

Risk of permanent RRT following CI-AKI

Following a case of CI-AKI there will be a small subset of people whose renal function will not recover and who will require permanent RRT. A study by James et al., (2011) reported the incidence of end-stage renal disease (ESRD; as defined by the requirement for dialysis or transplantation) following cases of CI-AKI, although this was not stratified according to CKD status. However, the study reports rates of CI-AKI in people with and without CKD, and the rates of ESRD per 100 person-years in people with and without CKD (see the full list of parameters in Table 33). From this, we estimate that the probability of transitioning to the permanent RRT state following CI-AKI is 4.08%. This is in reasonably close alignment with the figure used in the previous version of the model (3.28%; James et al., 2010); however we did not use this value as we were unable to replicate the calculations undertaken by the previous authors.

All-cause mortality following CI-AKI

We obtained mortality data from a European study of 1,490 people with CKD undergoing coronary angiography (Maioli et al., 2012; also see 'Baseline risk of CI-AKI' above). In total, 180 people experienced CI-AKI and 1,310 did not. In the 3 months following the coronary angiography, 13 people (7.22%) died in the CI-AKI group, while 18 people (1.37%) died in the no CI-AKI group. We used these data to calculate both the OR (5.59) and risk difference (5.85%) for mortality in the CI-AKI versus no CI-AKI group (Table 20). In the base case, we applied the OR to the background probability of death in people with CKD stage 3–5, thereby assuming there is a relative hazard of death associated with CI-AKI compared with no CI-AKI. In a sensitivity analysis, we applied the risk difference to the probability of death in CKD stage 3–5, assuming that there is an absolute excess hazard of death.

As well as the study by Maioli et al., (2012), we explored two additional sources of mortality data. A retrospective cohort study by Hoste et al., (2011) evaluated the epidemiology of CI-AKI in intensive care patients. Not all patients had CKD, so the study is not directly

applicable to our population of interest; however, it does allow us to explore mortality in a critically ill emergency population.

Finally, we extracted mortality data from the study by James et al., (2011) that was used to obtain the risk of permanent RRT following CI-AKI. Although the data were not reported directly, we were able to use the incidence of mortality in all patients (CKD and non-CKD), the proportion of people with CKD in the cohort, and the rate of mortality (per 100 person-years) in people with CKD to estimate the values needed (see the full list of parameters in Table 33 for values). A summary of mortality ORs and risk differences from all sources used within the model is presented in Table 20.

Table 20: Mortality following CI-AKI

Study	Deaths in CI-AKI group; n/N (%)	Deaths in no CI-AKI group; n/N (%)	Odds ratio	Risk difference
Maioli et al., 2012	13/180 (7.22%)	18/1310 (1.37%)	5.59	5.85%
Hoste et al., 2011	61/128 (47.66%)	123/659 (18.66%)	3.97	28.99%
James et al., 2011[a]	N/A	N/A	2.99	10.34%

(a) Mortality in CI-AKI group versus no CI-AKI group stratified according to CKD status was not reported, therefore odds ratios and risk differences were calculated using the incidence of mortality in all patients (CKD and non-CKD), the proportion of people with CKD in the cohort, and the rate of mortality (per 100 person-years) in people with CKD.

Probability of repeat scans

The previous version of the model used the probability of a repeat PCI as a surrogate for a repeat scan. The committee was happy with this approach, so we replicated it in our analysis. The annual probability of a repeat PCI used in the previous version of the model was 11.4%, taken from a study by Serruys et al., (2009); however, this study population was not specific to CKD. We identified a directly relevant Canadian study by Chan et al., (2015), investigating rates of repeat PCI in people with CKD who originally received PCI for revascularisation for multivessel disease. Of 893 patients who underwent the original procedure, 131 required repeat revascularisation over an average of 1.76 years of follow-up. From this, we calculated the per-cycle rate of repeat PCI to be 2.06%.

Treatment effects

An NMA was undertaken to combine direct and indirect evidence on the effectiveness of each intervention in preventing CI-AKI (see Appendix B – Methods and Appendix G – Network meta-analysis results). We obtained relative treatment effects from the NMA as log ORs (lnORs) versus no intravenous hydration. We re-expressed these lnORs as relative to oral NAC plus sodium chloride 0.9% by subtracting each of them from the lnOR for that strategy. We were then able to apply these lnORs to the base-case baseline risk of CI-AKI (11.5%; see 'Baseline risk of CI-AKI' above) to obtain the absolute odds of CI-AKI for each intervention. We then converted these odds to probabilities (Table 21). In sensitivity analyses, we explored numerous sources for the baseline risk of CI-AKI, each of which included different interventions (see above). We therefore altered the baseline intervention according to which was used in the source data and applied the relative treatment effects to the appropriate baseline risk.

Table 21: Treatment effects

Intervention	ln(OR) versus no IV hydration[a]	Probability of CI-AKI[b]
No (intravenous) hydration	-	18.54%
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	-0.821 (-1.86, 0.22)	9.10%
NAC (IV bolus) + sodium chloride 0.9% (IV)	-0.773 (-2.11, 0.56)	9.51%
NAC (IV) + sodium chloride 0.45% (IV)	-0.582 (-1.87, 0.71)	11.28%
NAC (IV) + sodium chloride 0.9% (IV)	-0.414 (-1.19, 0.36)	13.08%
NAC (oral)	0.036 (-1.45, 1.53)	19.10%
NAC (oral) + sodium bicarbonate (IV)	-0.472 (-1.26, 0.32)	12.43%
NAC (oral) + sodium chloride 0.45% (IV)	-0.615 (-1.66, 0.42)	10.95%
NAC (oral) + sodium chloride 0.9% (IV)	-0.560 (-1.27, 0.15)	11.51%
Oral fluids	-0.868 (-2.05, 0.32)	8.72%
Sodium bicarbonate (IV)	-0.610 (-1.26, 0.04)	11.01%
Sodium bicarbonate (oral) + oral fluids	-2.089 (-4.93, 0.75)	2.74%
Sodium chloride 0.45% (IV)	0.258 (-0.66, 1.18)	22.76%
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	0.551 (-1.45, 2.55)	28.30%
Sodium chloride 0.9% (IV)	-0.344 (-0.99, 0.30)	13.89%
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	-0.889 (-1.80, 0.02)	8.56%
Sodium citrate (oral)	0.134 (-1.41, 1.68)	20.65%

(a) Data are presented as mean (95% confidence intervals).
(b) Base case scenario; 11.5% baseline risk of CI-AKI with NAC (oral) plus sodium chloride 0.9% (Maioli et al., 2008).
CI-AKI, contrast-induced acute kidney injury; IV, intravenous; ln(OR), log odds ratio; NAC, N-acetylcysteine.

Resource use and costs

With some exceptions (described in detail below), we replicated the approach to resource use and costing used in the previous version of the guideline. We split the costs into 2 separate categories: fluid strategies and health states. As a general principle, if we were not able to obtain an error estimate for costs, we assumed the costs were fixed rather than assuming a standard error of 50% of the mean, as was done in the previous iteration of the model.

Fluid strategies: unit costs

The total cost of the fluid strategies incorporates unit costs of the interventions themselves, plus any associated healthcare resource use required for their administration. For intravenous (IV) fluids (sodium chloride 0.9% and 0.45%, and sodium bicarbonate), the previous developers obtained the unit costs either through personal communication from the commercial medicines unit (CMU) or from NHS list prices. We searched a number of sources (the British National Formulary [BNF], the CMU electronic market information tool [eMIT], the NHS Drug Tariff) and contacted the CMU to request costs with national discounts applied. We also inflated the costs used in the previous version of the model as an additional option. We then asked the committee to consider all the available cost estimates to assess which best reflected their experience. Based on committee advice that other costs appeared low, and given that costs were not always listed in the NHS Drug Tariff, we used NHS indicative

prices from the BNF as the base case and explored costs provided by the CMU in a sensitivity analysis (Table 22).

Other intervention components include NAC (oral capsules, IV bolus and solution for infusion), sodium bicarbonate capsules, oral sodium citrate and oral fluids. We assumed that there was no cost associated with oral fluids, as this involves asking people to drink a volume of water before their contrast procedure. For the other interventions, we obtained prices from CMU where possible (either personal communication or the eMIT), or alternatively from the NHS Drug Tariff if no price was available from the CMU. We were not able to find a cost for an IV bolus of NAC; therefore, we assumed the same cost as the infusion (Table 22).

Table 22: Intervention unit costs

Fluid	Volume/dose per unit	Cost per unit	Source
IV sodium chloride 0.45%	500 ml	£3.98	Joint Formulary Committee 2019 (Polyfusor SB)[a]
		£1.00	Commercial Medicines Unit, personal communication via email, June 2019[b]
IV sodium chloride 0.9%	500 ml	£2.70	Joint Formulary Committee 2019 (Polyfusor SB)[a]
		£0.75	Commercial Medicines Unit, personal communication via email, June 2019[b]
IV sodium chloride 0.9%	1000 ml	£3.59	Joint Formulary Committee 2019 (Polyfusor SB)[a]
		£0.92	Commercial Medicines Unit, personal communication via email, June 2019[b]
IV sodium bicarbonate	500 ml	£11.41	Joint Formulary Committee 2019 (Polyfusor sodium bicarbonate)[a]
Sodium bicarbonate capsules	500 mg	£0.02	Commercial Medicines Unit, 2019
Oral fluids	N/A	£0.00	N/A
Sodium citrate 0.3M (88.23 mg per 1 ml) oral solution	30 ml	£2.38	Commercial Medicines Unit, 2019
N-Acetylcysteine capsules	600 mg	£1.33	NHS Business Services Authority, 2019a
N-Acetylcysteine infusion ampoule (2g/10ml)	10 ml	£2.13	NHS Business Services Authority, 2019a
		£0.80	Commercial Medicines Unit, personal communication via email, June 2019[b]

(a) NHS indicative prices used when no tariff price was available.
(b) Explored as a sensitivity analysis.
BNF, British National Formulary; CMU, commercial medicines unit; IV, intravenous; NAC, N-acetylcysteine.

Fluid strategies: total costs

We used the same infusion strategy volumes and doses as the previous analysis. For interventions that were not previously analysed, we looked at the included trials from the clinical review to determine the appropriate volumes and doses. We varied our analysis slightly compared with the previous version in terms of base case assumptions surrounding hospital admission requirements for IV regimens. The guideline committee for CG169 advised the developers of the previous iteration of the model that regimens involving sodium chloride 0.9% and sodium bicarbonate (apart from the combination of the 2) could be delivered in under 8 hours and therefore did not require overnight hospital admission. However, we were advised by the committee that in most cases admission is required for all IV fluids, particularly in centres that do not have day units or for scans that occur early or late in the day. Therefore, in our base case all IV regimens require admission and therefore attract the cost of an excess bed day. We explored the assumptions from the previous model in a sensitivity analysis. In an additional sensitivity analysis, we assumed that none of the interventions required the cost of an excess bed day. This is to represent an inpatient population who would not encounter any excess bed day costs as a result of contrast administration. Table 23 summarises the components and costs of all intervention strategies.

Table 23: Intervention regimen components and total costs

Intervention	Components	Base case		SA1[a]		SA2[b]	
		Bed day required	Cost	Bed day required	Cost	Bed day required	Cost
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	- 1000 ml sodium chloride 0.9% - 4 x 600 mg NAC capsules - 1 x NAC infusion	Yes	£389.81	No	£11.04	No	£11.04
NAC (IV bolus) + sodium chloride 0.9% (IV)	- 1000 ml sodium chloride 0.9% - 1 x NAC infusion	Yes	£384.49	No	£5.72	No	£5.72
NAC (IV) + sodium chloride 0.45% (IV)	- 4 x 500 ml sodium chloride 0.45% - 1 x NAC infusion	Yes	£396.82	Yes	£396.82	No	£18.05
NAC (IV) + sodium chloride 0.9% (IV)	- 1000 ml sodium chloride 0.9% - 1 x NAC infusion	Yes	£384.49	No	£5.72	No	£5.72
NAC (oral)	- 4 x 600 mg NAC capsules	No	£5.32	No	£5.32	No	£5.32
NAC (oral) + sodium bicarbonate (IV)	- 2 x 500 ml sodium bicarbonate - 4 x 600 mg NAC capsules	Yes	£406.91	No	£28.14	No	£28.14
NAC (oral) + sodium chloride 0.45% (IV)	- 4 x 500 ml sodium chloride 0.45%	Yes	£400.01	Yes	£400.01	No	£21.24

Intervention	Components	Base case		SA1[a]		SA2[b]	
		Bed day required	Cost	Bed day required	Cost	Bed day required	Cost
	- 4 x 600 mg NAC capsules						
NAC (oral) + sodium chloride 0.9% (IV)	- 1000 ml sodium chloride 0.9% - 4 x 600 mg NAC capsules	Yes	£387.68	No	£8.91	No	£8.91
Oral fluids	N/A	No	£0.00	No	£0.00	No	£0.00
Sodium bicarbonate (IV)	- 2 x 500 ml sodium bicarbonate	Yes	£401.59	No	£22.82	No	£22.82
Sodium bicarbonate (oral) + oral fluids	- 16 x 500 mg sodium bicarbonate capsules[c]	No	£0.26	No	£0.26	No	£0.26
Sodium chloride 0.45% (IV)	- 4 x 500 ml sodium chloride 0.45%	Yes	£394.69	Yes	£394.69	No	£15.92
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	- 4 x 500 ml sodium chloride 0.45% - 2 x 500 ml sodium bicarbonate	Yes	£417.51	Yes	£417.51	No	£38.74
Sodium chloride 0.9% (IV)	- 1000 ml sodium chloride 0.9%	Yes	£382.36	No	£3.59	No	£3.59
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	- 1500 ml sodium chloride 0.9% - 2 x 500 ml sodium bicarbonate	Yes	£407.88	Yes	£407.88	No	£29.11
Sodium citrate (oral)	- 30 ml oral solution[d]	No	£2.38	No	£2.38	No	£2.38

IV, intravenous; NAC, N-acetylcysteine; SA, sensitivity analysis.
(a) Sensitivity analysis 1: same bed day/admission assumptions as previous version of model.
(b) Sensitivity analysis 2: inpatient population with no excess bed day costs.
(c) One study in the clinical review used oral sodium bicarbonate (Cho et al., 2010). The dose was 3.9 g given 20 minutes prior to contrast exposure followed by 1.95 g 2 hours and 4 hours after the initial dose. This resulted in a total dose of 7.8 g, requiring 16 x 500 mg capsules.
(d) One study in the clinical review used oral sodium citrate (Martin-Moreno et al., 2015). The dose was 1,380 mg/l of sodium at a rate of 75 ml/10 kg, divided into 4 doses (1 dose per hour).

We used the 2017–18 NHS Schedule of Reference Costs (NHS Improvement, 2018) to estimate the cost of an excess bed day. The previous developers assumed this was an excess bed day for currency code EA36A (Catheter 19 years and over); however, this code was not present in the most recent reference costs so we instead used a pooled average of

elective and non-elective excess bed days for cardiac catheterisation (currency codes EY42A–EY43F; pooled average £378.77).

Health states: costing overview

We took a similar approach to costing the health states as the previous model, again with some exceptions. As a general rule, any NHS reference costs were updated to 2017–18 values rather than 2010–11. We also obtained costs and resource data from the Personal Social Services Research Unit (Curtis & Burns, 2018), the British National Formulary (Joint Formulary Committee, 2019), the Commercial Medicines Unit (2019), the NHS Drug Tariff (NHS Business Services Authority, 2019a) and the NICE guideline on RRT and conservative management (NG107; NICE, 2018).

Health states: cost of CI-AKI

The total cost of a cycle in the CI-AKI state consisted of treatment for the AKI, temporary dialysis for a small proportion of people who require it, and permanent RRT for those who progress to RRT following their CI-AKI. We obtained the cost of the AKI treatment and dialysis from NHS reference costs (2017–18). We found 3 studies that report the number of people requiring temporary dialysis following CI-AKI (Kama et al., 2014; Briguori et al., 2002; Briguori et al., 2007); we pooled numbers from each study to calculate the odds and probability of requiring temporary dialysis (4 out of 16 people in Kama et al., 2014; 1 out of 16 people in Briguori et al., 2002; 2 out of 13 people in Briguori et al., 2007). From this, we obtained a probability of 17.53%. We consulted the committee regarding the number of dialysis sessions usually received by people who require temporary dialysis following CI-AKI. We were advised that people usually have 1–3 sessions, and that these sessions are almost always haemodialysis rather than peritoneal dialysis. The cost of CI-AKI is summarised in Table 24. A more detailed summary of the permanent RRT costs is reported in the 'Health states: cost of RRT' section.

Table 24: CI-AKI costs and resource use

	Value	Source
AKI costs		
Pooled average cost of AKI	£1,865	NHS Improvement, 2018 (NHS reference costs 2017–18, pooled average of LE07H, J, K, L, M, N, P)
Temporary RRT costs		
Probability of requiring temporary RRT	17.53%	Pooled from:[a] Kama et al., 2014 Briguori et al., 2002 Briguori et al., 2007
Number of dialysis sessions required for temporary RRT	2	Committee assumption, 2019[b]
Cost of a haemodialysis session for RRT	£271	NHS Improvement, 2018 (NHS reference costs 2017–18, LE01A)
Total cost of temporary dialysis for CI-AKI	£94.99	Calculation[c]
Permanent RRT costs		
Cost of permanent RRT following CI-AKI	£1,657	Calculation[d]

	Value	Source
Total cost of CI-AKI	**£3,617**	Calculation[e]

(a) Numbers from each study were pooled to calculate the odds and probability of requiring temporary dialysis (4 out of 16 people in Kama et al., 2014; 1 out of 16 people in Briguori et al., 2002; 2 out of 13 people in Briguori et al., 2007).
(b) Triangular distribution used to vary this value between 1 and 3.
(c) Calculated by multiplying the probability of requiring temporary RRT by the number of dialysis sessions required and the cost per session.
(d) Calculated by multiplying the cost of permanent RRT (as described in the 'Health states: RRT' section) by the probability of progressing to RRT following CI-AKI (4.08%). Includes the costs of RRT for one cycle.
(e) Cost of AKI plus cost of temporary RRT plus cost of permanent RRT.

Health states: cost of CKD stages 3–5 (pre-dialysis)

Costs associated with the CKD stages 3–5 (pre-dialysis) state include nephrology appointments, estimated glomerular filtration rate (eGFR) measurements (consisting of one biochemistry and one phlebotomy test), treatment for anaemia (with epoetin), diuretics, and home and telephone consultations with a nurse (Table 25). We took assumptions surrounding the resource use (e.g. the number of appointments), as well as epoetin and furosemide requirements, from the previous version of the guideline (NICE, 2013a). In terms of the proportion of people in each CKD stage, the previous committee advised that 70% of people were in stage 3, 25% were in stage 4 and 5% were in stage 5 (NICE, 2013a). Of those in stage 5, 39% were assumed to not be on RRT (Hussain et al., 2013). As people on RRT are not included in this health state, the remaining proportions are 72.2% in stage 3, 25.8% in stage 4, and 2.0% in stage 5 (pre-dialysis). We grouped stages 3 and 4 together for costing purposes, while we assume that stage 5 requires greater resource use (e.g. more nephrology appointments per cycle) and therefore attracts a greater cost.

Table 25: CKD stages 3–5 costs and resource use

	Value	Source
Stages 3 and 4		
Number of nephrology appointments per cycle	1	NICE, 2013a (committee assumption)
Total cost of nephrology appointments	£181.11	NHS Improvement, 2018 (NHS reference costs 2017–18, WF01B, nephrology)
Number of eGFR measurements per cycle	1	NICE, 2013a (committee assumption)
Total cost of eGFR measurements	£3.94	NHS Improvement, 2018 (NHS reference costs 2017–18, DAPS04 + DAPS08)
Proportion of people with anaemia (receiving epoetin)	9%	NICE, 2013a
Total cost of epoetin per cycle	£21.61	Calculation[a]
Proportion receiving furosemide (stage 4 only)	60%	NICE, 2013a
Total cost of furosemide per cycle	£1.37	Calculation[b]
Total cost of stages 3 and 4	£208.04	Calculation[c]
Stage 5 (pre-dialysis)		
Number of nephrology appointments per cycle	2	NICE, 2013a (committee assumption)

	Value	Source
Total cost of nephrology appointments	£362.22	NHS Improvement, 2018 (NHS reference costs 2017–18, WF01B, nephrology)
Number of eGFR measurements per cycle	13.04	NICE, 2013a (committee assumption)
Total cost of eGFR measurements	£51.41	NHS Improvement, 2018 (NHS reference costs 2017–18, DAPS04 + DAPS08)
Proportion of people with anaemia (receiving epoetin)	33%	NICE, 2013a
Total cost of epoetin per cycle	£80.05	Calculation[a]
Proportion receiving furosemide (stage 4 only)	90%	NICE, 2013a
Total cost of furosemide per cycle	£1.70	Calculation[d]
Number of nurse phone appointments	13.04	NICE, 2013a (committee assumption)
Total cost of nurse phone appointments per cycle	£80.44	Calculation[e]
Number of nurse home visits	3	NICE, 2013a (committee assumption)
Total cost of nurse home visits per cycle	£92.50	Calculation[e]
Total cost of stage 5 (pre-dialysis) per cycle	£668.32	Calculation[f]
Proportions in each stage		
Stage 3	72.20%	Calculation[g]
Stage 4	25.79%	Calculation[g]
Stage 5 (pre-dialysis)	2.01%	Calculation[g]
Total cost of stages 3–5 CKD	**£217.30**	Calculation[h]

a) *Average cost of one unit of Eprex is £0.01 (NHS Business Services Authority, 2019a). Average weekly dose 1,788 units (NICE, 2015; cost-effectiveness appendix). Per cycle costs obtained by multiplying the weekly dose by the cycle length (in weeks), then by the cost per unit and the percentage with anaemia.*
b) *Cost of a 40 mg tablet of furosemide is £0.03 (Commercial Medicines Unit, 2019). Assumed dose is 40 mg per day (NICE, 2013a). Total cost obtained by multiplying the cost for one tablet by the number of days in a cycle, followed by the percentage receiving furosemide.*
c) *Total cost of nephrology appointments, eGFR tests, epoetin and furosemide.*
d) *Cost of a 40 mg tablet of furosemide is £0.03 (Commercial Medicines Unit, 2019). Assumed dose is 80 mg per day (NICE, 2013a). Total cost obtained by multiplying the cost for two tablets by the number of days in a cycle, followed by the percentage receiving furosemide.*
e) *Cost of an hour of specialist clinical nurse time (band 6) was £74 (Curtis & Burns, 2018). Each phone appointment was assumed to last 6 minutes and each home visit was assumed to last 25 minutes (committee assumption from 2013 guideline).*
f) *Total cost of nephrology appointments, eGFR tests, epoetin, furosemide, home visits and phone appointments.*
g) *Proportions in each stage (3, 4 or 5) sourced from previous committee advice. Those in stage 5 who were on RRT (61%; Hussain et al., 2013) were removed from the proportions.*
h) *Total costs of stages 3–4 CKD and costs of stage 5 CKD weighted by the percentages in each stage.*

Health states: cost of RRT

Our approach to costing RRT is heavily based on the RRT guideline (NG107; NICE 2018). Costs within the RRT state consist of appointments, eGFR tests, treatment for anaemia (with epoetin), and costs of the RRT split into dialysis and transplantation. We assume that all patients attract the costs of appointments, eGFR tests and treatment for anaemia, while a proportion of people will have dialysis for the remainder of their lives (either haemodialysis or peritoneal dialysis), and the remainder will receive a transplant. We obtained the overall

probability of being waitlisted from the NHS Organ Donation and Transplantation Activity Report (NHS Blood and Transplant, 2018), which we converted to the odds of being waitlisted. We obtained the odds ratios for being wait-listed according to age from the UK Renal Registry (2018). This only went up to age 64, so we used linear extrapolation to calculate the odds ratios for higher age brackets. We used the overall odds of being wait listed and the odds ratios according to age to obtain the probability of being wait-listed for each age group. We obtained the proportions of people on haemodialysis versus peritoneal dialysis from the renal registry (UK Renal Registry, 2018).

Dialysis costs involve an initial access procedure followed by the ongoing costs of dialysis sessions, plus an assumption that 15% of the total dialysis costs are for travel, access maintenance, and other associated costs (NICE, 2018). Transplantation costs include the cost of the transplant itself, plus ongoing immunosuppression. The approach to costing the transplant procedure was adapted from the NICE guideline for renal replacement therapy and conservative management (NICE, 2018), apart from the cost of associated appointments which were already accounted for via the cost of nephrology consultations. The approach to costing immunosuppressant therapy was adapted from the guideline for the management of hyperphosphataemia in chronic kidney disease (NICE, 2013b). As part of this, we assume a one-off induction with basiliximab costing £2,162, followed by ongoing maintenance therapy with azathioprine plus either tacrolimus or ciclosporin costing an average of £1,643 per cycle. See the full parameter table for unit costs of immunosuppressant therapy (Table 33).

Given that we were adapting the model structure from the previous iteration, which did not include transplantation as part of the RRT costs, it was necessary to add or subtract some costs up-front (within the first cycle after entering the RRT state) to ensure the correct proportion of people encountered the costs of transplantation and dialysis at the correct timepoints. Our approach to transplantation costs is summarised below:

- Cycle 1
  - Apply a one-off cost of transplantation to the proportion of people who are likely to receive a transplant over their lifetime (54%; UK Renal Registry, 2018), discounted at the average transplant waiting list time.
  - Apply the costs of dialysis for the time period up to transplantation, with the assumption that the people who do eventually receive a transplant receive dialysis while they are on the waiting list. We discount these dialysis costs continuously up to the point of transplantation.
  - People who have a transplant will require immunosuppressant drugs. We subtract the cost of immunosuppressants from the point of RRT initiation to the time of transplant as part of the cycle 1 costs. This is because people who eventually receive a transplant will start to accrue immunosuppressant costs as soon as they enter cycle 2. Unless we subtract some immunosuppressant costs up-front, people will accrue immunosuppressant costs for the time period before they have the transplant and the costs will be overestimated.
  - Similarly, we have added the costs of immunosuppressants for one cycle within cycle 1 so that immunosuppressants for the cycle directly following the time of transplant are incorporated.
- Cycle 2 onwards
  - Apply the costs of ongoing immunosuppressants to the proportion of people who receive a transplant (54%).

Table 26 provides a full summary of RRT costs split according to cycle 1 or cycle 2 onwards.

Table 26: RRT costs and resource use

Cycle 1	Value	Source
All patients		
Number of first nephrology appointments per cycle	1	NICE, 2013a (committee assumption)
Number of follow-up nephrology appointments per cycle	1	NICE, 2013a (committee assumption)
Total cost of nephrology appointments	£414.39	NHS Improvement, 2018 (NHS reference costs 2017–18, WF01B + WF01A nephrology)
Number of eGFR measurements per cycle	13.04	NICE, 2013a (committee assumption)
Total cost of eGFR measurements	£51.41	NHS Improvement, 2018 (NHS reference costs 2017–18, DAPS04 + DAPS08)
Proportion of people with anaemia (receiving epoetin)	33%	NICE, 2013a
Total cost of epoetin per cycle	£80.05	Calculation[a]
Total cost of appointments and tests	£545.85	Calculation
Dialysis patients		
Proportion haemodialysis vs peritoneal	87%	UK Renal Registry, 2018
Frequency of haemodialysis per week	3	UK Renal Registry, 2018
Cost of haemodialysis session	£153.36	NHS Improvement, 2018 (NHS reference costs 2017–18, pooled average of LD01A, 02A, 03A, 04A, 05A, 06A, 07A, 08A, 09A, 10A)[b]
Cost of haemodialysis initial access procedure	£1,842.45	NHS Improvement, 2018 (NHS reference costs 2017–18, pooled average of YR41A and YQ42Z)
Frequency of peritoneal dialysis per week	7	UK Renal Registry, 2018
Cost of peritoneal dialysis session	£74.35	NHS Improvement, 2018 (NHS reference costs 2017–18, pooled average of LD11A, 12A, 13A)[b]
Cost of peritoneal dialysis associated procedures	£860.00	NHS Improvement, 2018 (NHS reference costs 2017–18, LD05Z)
Proportion of total dialysis costs for travel, access maintenance, etc.	15%	NICE, 2018 (committee assumption)
Per cycle average cost of dialysis	£7,181	Calculation[c]
Cost of initial access procedures	£1,714.31	Calculation[d]
Total cost of dialysis, first cycle	£8,895.63	Calculation[e]
Transplant recipients		
Waiting time to transplant (years)	2.14	NHS Blood and Transplant, 2018
Discounted waiting time to transplant (years)	2.06	Calculation[f]

Cycle 1	Value	Source
Cost of kidney transplant	£16,663	NHS Improvement, 2018 (NHS reference costs 2017–18, LA11Z, LA12A, LB46Z, LA01A, LA02A, LA03A)[g]
Discounted cost of kidney transplant	£15,479	Calculation[h]
Cost of dialysis (over waiting list period)	£59,291	Calculation[f]
Cost of immunosuppressants (one cycle)	£3,651	Calculation[h]
Cost of immunosuppressants (from state entry to time of transplant)	£13,562	Calculation[f]
Total cost of transplant, first cycle	£66,574	Calculation[i]
Total cost of RRT cycle 1	**£40,588[j]**	Calculation[k]
Cycle 2 onwards		
All patients		
Number of follow-up nephrology appointments per cycle	2	NICE, 2013a (committee assumption)
Total cost of nephrology appointments	£362.22	NHS Improvement, 2018 (NHS reference costs 2017–18, WF01A nephrology)
Number of eGFR measurements per cycle	13.04	NICE, 2013a (committee assumption)
Total cost of eGFR measurements	£51.41	NHS Improvement, 2018 (NHS reference costs 2017–18, DAPS04 + DAPS08)
Proportion of people with anaemia (receiving epoetin)	33.33%	NICE, 2013a (committee assumption)
Total cost of epoetin per cycle	£80.05	Calculation[a]
Total cost of appointments and tests	£493.68	Calculation
Dialysis patients		
Total dialysis costs (per cycle)	£7,181	Calculation (see cycle 1)
Transplant recipients		
Ongoing immunosuppressant costs	£1,643	Calculation
Total cost of RRT cycle 2	**£4,684[j]**	**Calculation[j]**

a) *Average cost of one unit of Eprex is £0.01 (NHS Business Services Authority, 2019a). Average weekly dose 1,788 units (NICE, 2015; cost-effectiveness appendix). Per cycle costs obtained by multiplying the weekly dose by the cycle length (in weeks), then by the cost per unit and the percentage with anaemia.*
b) *Costing in alignment with the NICE guideline on renal replacement therapy and conservative management (NICE, 2018). Costs away from base incorporated within the average where available.*
c) *Frequency of dialysis (sessions per month) multiplied by the cost of a session, weighted by the proportions in haemodialysis vs peritoneal dialysis.*
d) *Costs of the access procedures weighted by the type of dialysis.*
e) *Dialysis sessions plus access procedures.*
f) *Time discounted using an instantaneous discount rate of 3.44%. Discounted time used as the discount factor for ongoing costs accrued until the time of transplant.*
g) *Activity numbers used to determine numbers of live donors for weighting of costs.*
h) *Discounted at the transplant waiting list time at a rate of 3.5%.*
i) *Cost of transplant, dialysis initiation costs, ongoing dialysis costs, plus one cycle of immunosuppressants, minus the cost of immunosuppression to the point of transplant.*
j) *Reported cost is for somebody aged 70 years. This cost will change as the probability of receiving a transplant changes with age.*
k) *Total cost of appointments, eGFR tests, epoetin, and weighted costs of dialysis and transplantation.*

Quality of life

We were able to find utility values that were more appropriate for our modelled population compared with those used in the previous model. We sourced utility values for CKD stages 3, 4 and 5 (pre-dialysis) from a recent UK study by Jesky et al., (2016), while we obtained the RRT values from a study by Liem et al., (2008), which is in alignment with the NICE clinical guideline on renal replacement therapy and conservative management (NICE, 2018). We did not vary the proportions of people in each of the RRT states by age (as we did for the costs); the proportions were obtained from the UK Renal Registry (2018); 46% of people are on dialysis compared with transplant. Of those who are on dialysis, 87% are receiving haemodialysis and the remaining 13% are receiving peritoneal dialysis.

We were unable to find an appropriate study that reported utility values for CI-AKI in a UK population with CKD. We instead used a Finnish study that reported quality of life measured using the EQ-5D in critically ill people with all types of AKI (Nisula et al., 2013). The study reports utility values at 6 months after admission to intensive care in study participants with AKI and in age- and sex-matched controls. From this, we were able to calculate the relative utility decrement associated with an episode of AKI and apply it to population utility norms (Kind et al., 1999).

Table 27: Utility values

Health state	Utility values[a]	Source
Chronic kidney disease		
Stage 3	0.80 (0.69, 1.00)	Jesky et al., 2016
Stage 4	0.74 (0.62, 0.85)	Jesky et al., 2016
Stage 5, pre-dialysis	0.73 (0.62, 1.00)	Jesky et al., 2016
Stage 5, haemodialysis	0.56 (0.49, 0.62)	Liem et al., 2008
Stage 5, peritoneal dialysis	0.58 (0.50, 0.67)	Liem et al., 2008
Stage 5, transplanted	0.81 (0.72, 0.90)	Liem et al., 2008
Acute kidney injury		
EQ-5D index at 6 months, AKI	0.68 (0.52, 1.00)	Nisula et al., 2013
EQ-5D index at 6 months, no AKI	0.83 (0.81, 0.86)	Nisula et al., 2013
Population norms		
Men		
age < 25	0.94 (0.92, 0.96)	Kind et al., 1999
24 < age < 35	0.93 (0.91, 0.95)	Kind et al., 1999
34 < age < 45	0.91 (0.89, 0.93)	Kind et al., 1999
44 < age < 55	0.84 (0.80, 0.87)	Kind et al., 1999
54 < age < 65	0.78 (0.74, 0.82)	Kind et al., 1999
64 < age < 75	0.78 (0.74, 0.82)	Kind et al., 1999
74 < age	0.75 (0.70, 0.80)	Kind et al., 1999
Women		
age < 25	0.94 (0.92, 0.96)	Kind et al., 1999
24 < age < 35	0.93 (0.92, 0.94)	Kind et al., 1999
34 < age < 45	0.91 (0.89, 0.93)	Kind et al., 1999

Health state	Utility values[a]	Source
44 < age < 55	0.85 (0.82, 0.88)	Kind et al., 1999
54 < age < 65	0.81 (0.78, 0.84)	Kind et al., 1999
64 < age < 75	0.78 (0.75, 0.81)	Kind et al., 1999
74 < age	0.71 (0.67, 0.75)	Kind et al., 1999

(a) Utility values are mean (95% confidence intervals).

Sensitivity analyses

In order to explore uncertainty in model results, we conducted both deterministic and probabilistic sensitivity analyses.

Deterministic sensitivity analysis

Deterministic analyses either use alternative point estimates for model parameters or test different structural assumptions, in order to investigate the impact on results. The parameters of interest for deterministic sensitivity analysis in the current analysis included:

- Baseline risk of CI-AKI
- All-cause mortality following CI-AKI
- Probability of repeat scans
- Assumptions surrounding excess bed day costs

Further to this, we conducted a one-way sensitivity in which all parameters were varied between plausible bounds to determine which have the potential to affect cost-effectiveness results. Finally, we conducted scenario analyses in which we vary 2 or more parameters concurrently. This involved repeating the sensitivity analyses listed above while altering other parameters to represent emergency and elective populations:

- Emergency scenario: risk of CI-AKI taken from emergency studies and no excess bed day costs (represents a high-risk inpatient population)
- Elective scenario: risk of CI-AKI taken from elective studies, base-case excess bed day cost assumptions (represents a low-risk outpatient population)

Probabilistic sensitivity analyses

We configured the model to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We assigned probability distributions reflecting uncertainty surrounding point estimates to model input parameters. These were defined by standard error/confidence intervals and type of parameter. We sourced distribution parameters from the study in which the value was obtained, where possible, or estimated them based on the usual properties of data of that type. The model draws a random value from each of these distributions for 1,000 iterations and, for each of these iterations, records costs and QALYs for each strategy. This process allows uncertainty around model results to be characterised in terms of the proportion of iterations in which each comparator provides the optimal balance of costs and QALYs at a particular threshold. We can then construct cost-effectiveness acceptability curves (CEACs) to represent these results visually.

The particular distribution assigned to each type of model parameter reflects the nature of the data. As a rule, we use beta distributions to parameterise probabilities, to reflect the fact that these values must lie between 0 and 1. Although the majority of costs within the current model were fixed, some are given a gamma distribution, as these values are bound at 0 but theoretically have no upper limit. We assign a lognormal distribution to relative risks, ORs

and hazard ratios, in order to reflect the fact that these parameters are asymmetrically distributed (i.e. values between 0 and 1 favour one comparator, whereas values between 1 and infinity favour the other). As with probabilities, we assign utilities a beta distribution, as they are bounded at 1. For the treatment effects drawn from the NMA, we directly sampled from the WinBUGS CODA output (the posterior estimates of log-odds ratios) to preserve correlation between treatment effects for different interventions.

Original cost–utility model – results

Clinical outcomes

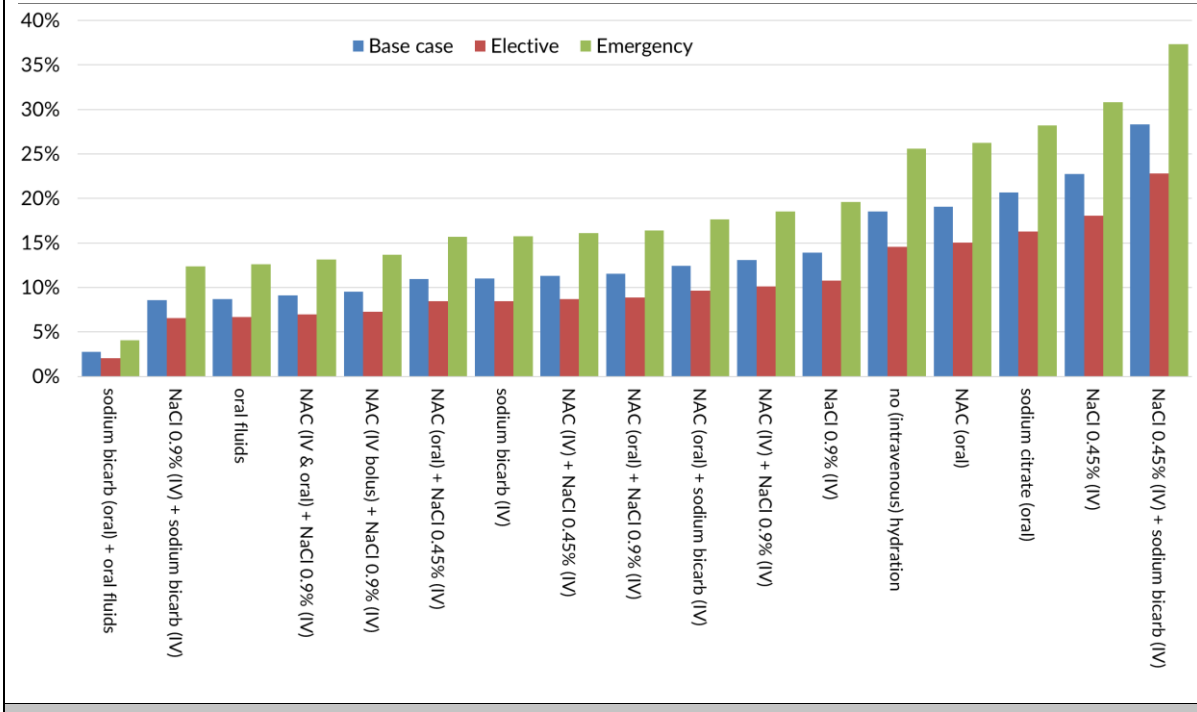
In terms of clinical outcomes, we investigated life-years, rates of CI-AKI, deaths from CI-AKI, progression to ESRD following CI-AKI and numbers of people progressing to ESRD overall for each intervention (Table 28). Results for all clinical outcomes reflect the NMA outputs, with the most effective intervention (sodium bicarbonate + oral fluids) resulting in the greatest

number of life-years, and lowest rates of CI-AKI, deaths, ESRD and lifetime RRT. The trends from the NMA continue across all results.

Table 28: Results – clinical outcomes

Name	Life-years	Rates of CI-AKI			CI-AKI deaths	ESRD following CI-AKI	Lifetime RRT
		First scan	Later scans	Lifetime scans			
No (intravenous) hydration	10.553	18.5%	14.7%	33.3%	1.9%	1.4%	3.8%
NAC (IV & oral) + NaCl 0.9% (IV)	10.648	9.1%	7.4%	16.5%	0.9%	0.7%	3.7%
NAC (IV bolus) + NaCl 0.9% (IV)	10.644	9.5%	7.7%	17.2%	1.0%	0.7%	3.7%
NAC (IV) + NaCl 0.45% (IV)	10.626	11.3%	9.1%	20.4%	1.2%	0.8%	3.8%
NAC (IV) + NaCl 0.9% (IV)	10.608	13.1%	10.5%	23.6%	1.3%	1.0%	3.8%
NAC (oral)	10.547	19.1%	15.2%	34.3%	1.9%	1.4%	3.8%
NAC (oral) + bicarb (IV)	10.614	12.4%	10.0%	22.4%	1.3%	0.9%	3.8%
NAC (oral) + NaCl 0.45% (IV)	10.629	11.0%	8.8%	19.8%	1.1%	0.8%	3.7%
NAC (oral) + NaCl 0.9% (IV)	10.624	11.5%	9.3%	20.8%	1.2%	0.8%	3.8%
Oral fluids	10.652	8.7%	7.0%	15.8%	0.9%	0.6%	3.7%
Bicarb (IV)	10.629	11.0%	8.9%	19.9%	1.1%	0.8%	3.8%
Bicarb (oral) + oral fluids	10.713	2.7%	2.2%	5.0%	0.3%	0.2%	3.7%
NaCl 0.45% (IV)	10.511	22.8%	18.0%	40.7%	2.3%	1.7%	3.9%
NaCl 0.45% (IV) + bicarb (IV)	10.456	28.3%	22.1%	50.4%	2.8%	2.1%	3.9%
NaCl 0.9% (IV)	10.599	13.9%	11.1%	25.0%	1.4%	1.0%	3.8%
NaCl 0.9% (IV) + bicarb (IV)	10.653	8.6%	6.9%	15.5%	0.9%	0.6%	3.7%

We explored the rates of CI-AKI following a first scan depending on the initial level of risk (base case [all], elective only or emergency only; Figure 9). The lowest rates were in the elective population, while the highest rates were in the emergency population. This is a direct reflection of the different estimates used for the baseline risk of CI-AKI.



IV, intravenous; NAC, N-acetylcysteine; NaCl, sodium chloride.

Figure 9: Initial rates of CI-AKI according to baseline risk

Base-case cost–utility results

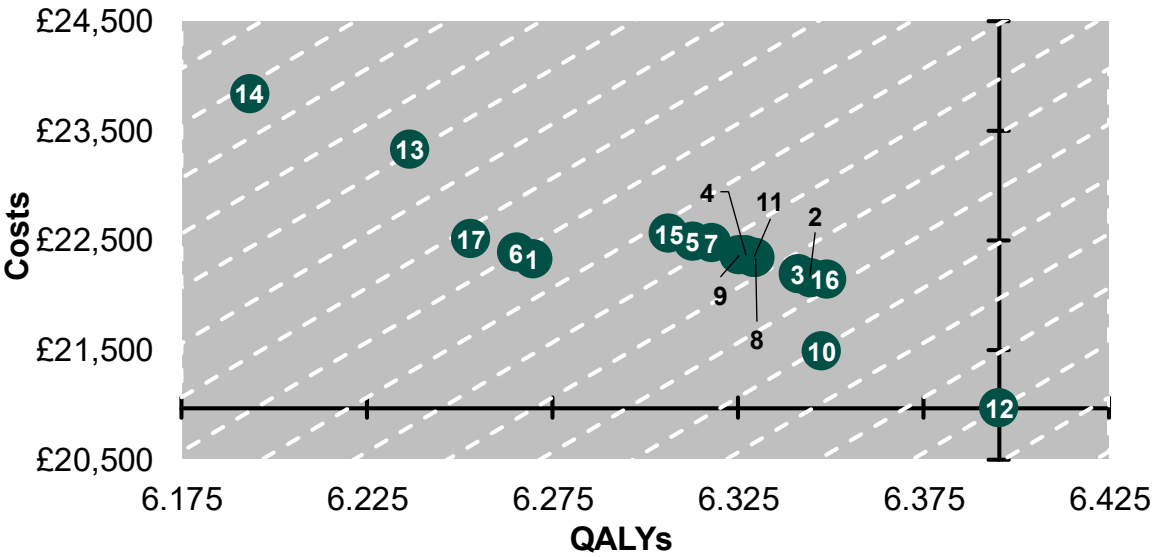
In the base-case deterministic results, sodium bicarbonate (oral) + oral fluids dominates all other interventions. It has an overall cost of £20,972 and results in 6.395 QALYs. All other interventions are found to be more expensive and less effective. Again, the results directly reflect the NMA outputs, indicating that the risk of CI-AKI is the key parameter underpinning the model.

Table 29: Base-case deterministic cost–utility results

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	Costs (£)	
sodium bicarbonate (oral) + oral fluids	£20,972	6.395				5.347
oral fluids	£21,489	6.347	£518	-0.0479	dominated	5.273
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£22,147	6.349	£1,175	-0.0466	dominated	5.241
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£22,164	6.344	£1,193	-0.0510	dominated	5.236
NAC (IV bolus) + sodium chloride 0.9% (IV)	£22,190	6.341	£1,219	-0.054	dominated	5.232
no (intravenous) hydration	£22,334	6.270	£1,362	-0.126	dominated	5.153
NAC (oral) + sodium chloride 0.45% (IV)	£22,340	6.330	£1,368	-0.066	dominated	5.213

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	Costs (£)	
sodium bicarbonate (IV)	£22,347	6.329	£1,375	-0.066	dominated	5.212
NAC (IV) + sodium chloride 0.45% (IV)	£22,363	6.327	£1,391	-0.068	dominated	5.209
NAC (oral) + sodium chloride 0.9% (IV)	£22,367	6.325	£1,395	-0.070	dominated	5.207
NAC (oral)	£22,390	6.265	£1,418	-0.130	dominated	5.146
NAC (oral) + sodium bicarbonate (IV)	£22,478	6.318	£1,506	-0.077	dominated	5.194
NAC (IV) + sodium chloride 0.9% (IV)	£22,496	6.313	£1,525	-0.083	dominated	5.188
sodium citrate (oral)	£22,518	6.253	£1,546	-0.142	dominated	5.127
sodium chloride 0.9% (IV)	£22,563	6.306	£1,591	-0.089	dominated	5.178
sodium chloride 0.45% (IV)	£23,337	6.236	£2,366	-0.159	dominated	5.070
sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£23,842	6.193	£2,871	-0.202	dominated	5.001

These results can be visualised on the cost-effectiveness plane (Figure 10). The intervention with the lowest cost is placed at the origin (sodium bicarbonate [oral] + oral fluids). All other interventions are located within the north west quadrant in comparison; therefore, all are dominated.



(1) no (intravenous) hydration
(2) NAC (IV bolus & oral) + sodium chloride 0.9% (IV)
(3) NAC (IV bolus) + sodium chloride 0.9% (IV)
(4) NAC (IV) + sodium chloride 0.45% (IV)
(5) NAC (IV) + sodium chloride 0.9% (IV)
(6) NAC (oral)
(7) NAC (oral) + sodium bicarbonate (IV)
(8) NAC (oral) + sodium chloride 0.45% (IV)
(9) NAC (oral) + sodium chloride 0.9% (IV)
(10) oral fluids
(11) sodium bicarbonate (IV)
(12) sodium bicarbonate (oral) + oral fluids
(13) sodium chloride 0.45% (IV)
(14) sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
(15) sodium chloride 0.9% (IV)
(16) sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
(17) sodium citrate (oral)

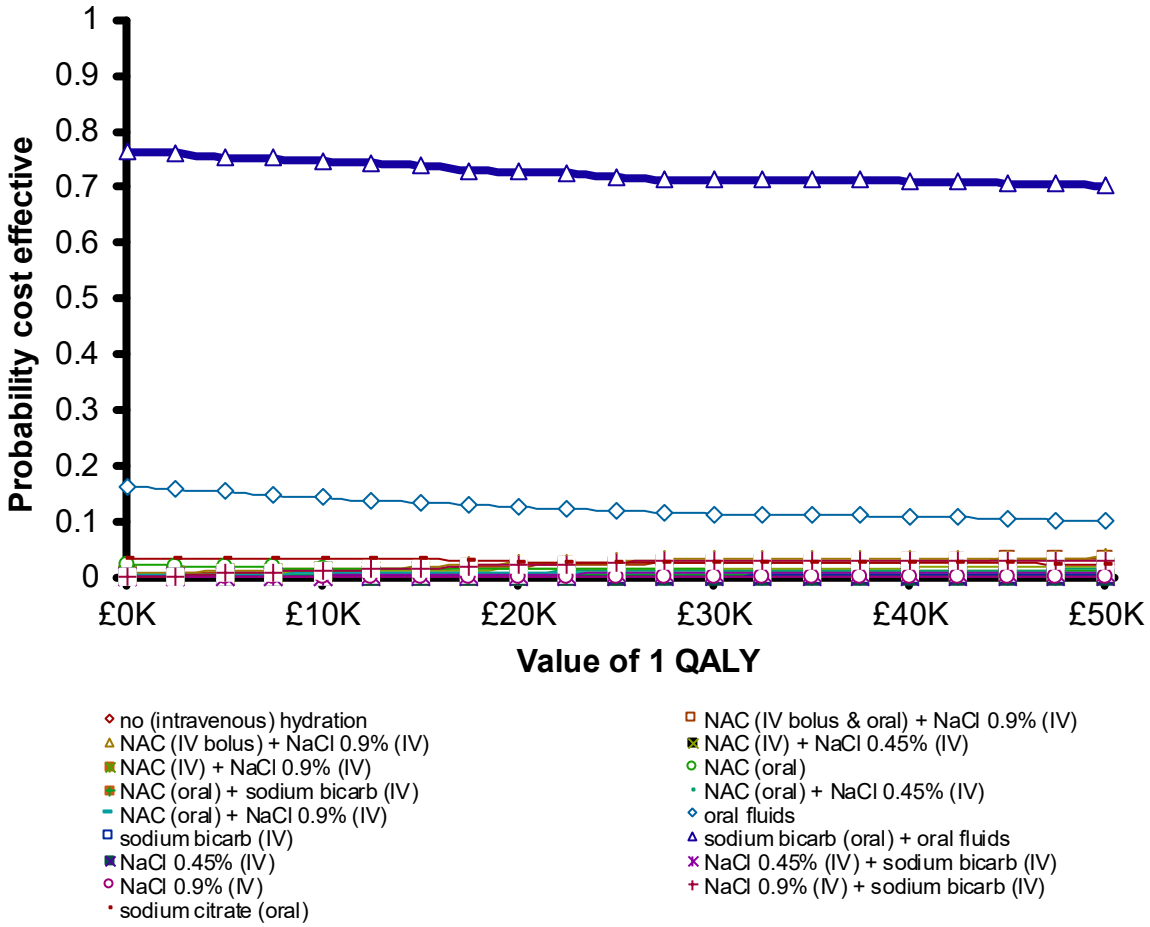
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY

Figure 10: Base-case deterministic cost–utility plane

Sensitivity analysis

Probabilistic sensitivity analysis

The CEAC (Figure 11) shows that, at all values of a QALY, sodium bicarbonate (oral) + oral fluids has the highest probability of being cost effective. As indicated by the cost-effectiveness acceptability frontier (the bold line), the same strategy has the highest expected net benefit at all QALY values.

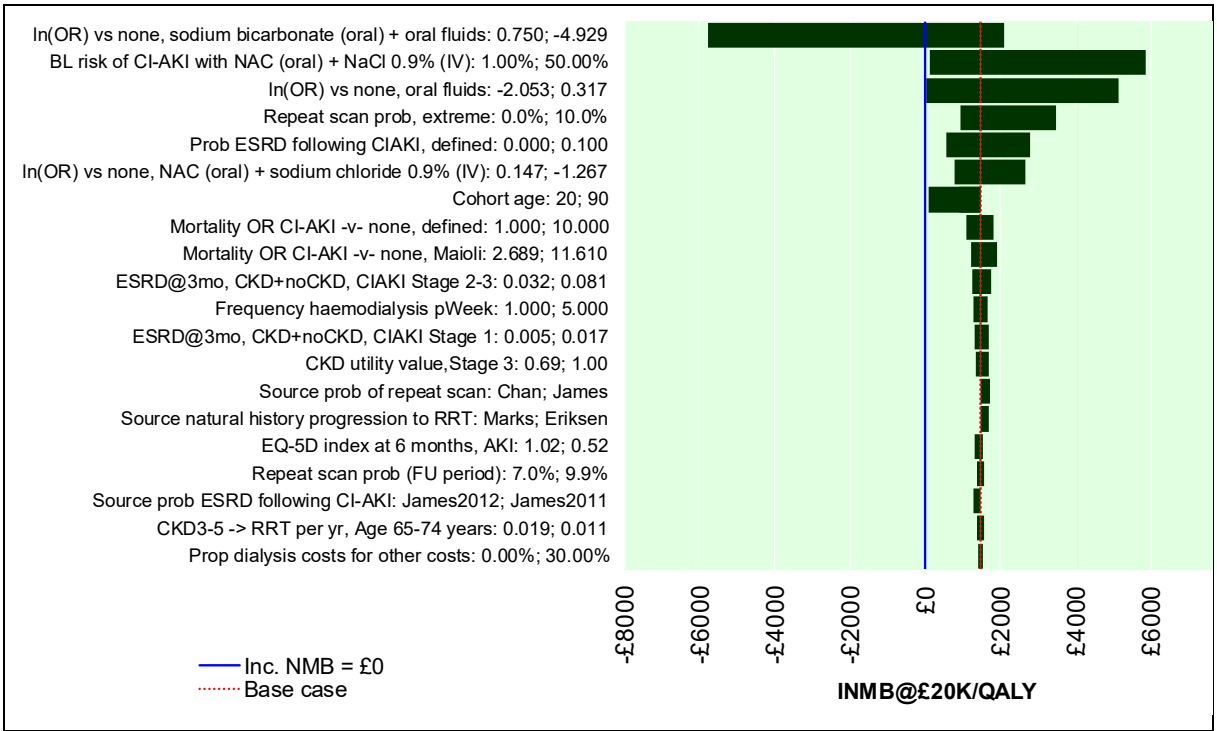


Bold line indicates cost-effectiveness acceptability frontier

Figure 11: Cost-effectiveness acceptability curve

One-way sensitivity analysis

Figure 12 presents the results of the one-way sensitivity analysis for sodium bicarbonate (oral) + oral fluids versus oral fluids alone (i.e. the most cost-effective intervention compared with the second most cost-effective). The parameter that has the greatest effect on cost-effectiveness results is the relative effect of sodium bicarbonate (oral) + oral fluids versus no intervention. The 95% credible interval for this parameter was wide, given the high degree of uncertainty surrounding the point estimate; therefore, when varied between the limits of the interval, this parameter has the potential to result in a negative incremental net monetary benefit. No other parameters, when varied, have the possibility of changing the cost-effectiveness conclusion.



INMB = incremental net monetary benefit
20 most influential parameters shown

Figure 12: One-way sensitivity analysis – sodium bicarbonate (oral) + oral fluids versus oral fluids alone

Other sensitivity analyses

We varied other parameters as described in the methods section. These include:

- Using mortality data from a non-CKD population who are critically ill (Hoste et al., 2011) and applying an absolute (rather than relative) risk of mortality. This affected the absolute numbers of costs and QALYs, but did not affect the conclusions of the incremental analysis.
- Varying the probability of repeat scans, which did not have a notable impact on results.

Scenario analysis

Without sodium bicarbonate (oral) + oral fluids

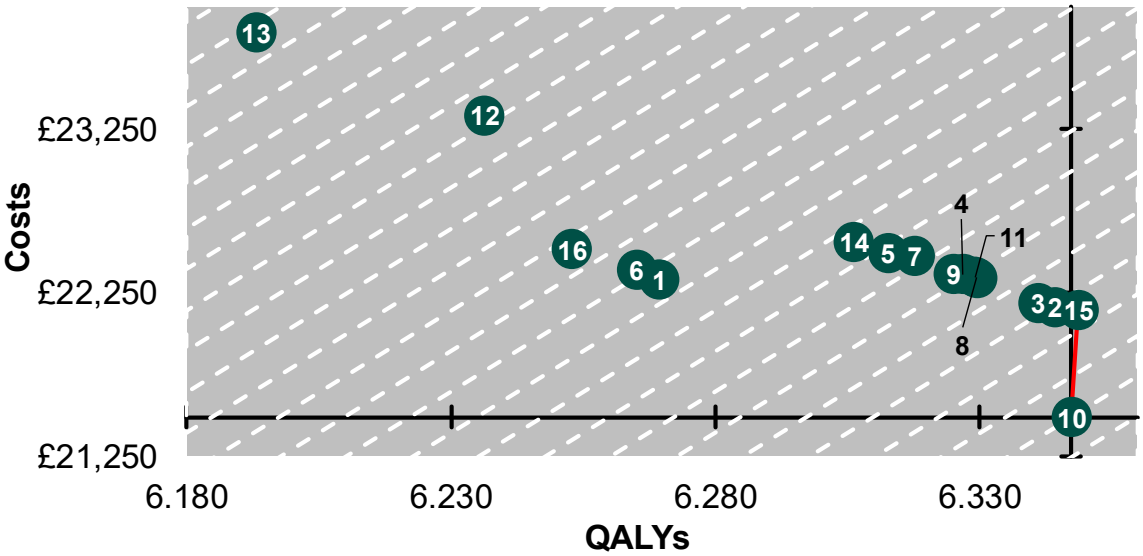
Although sodium bicarbonate (oral) + oral fluids was associated with the most positive point-estimate in the NMA and base-case cost-effectiveness results, the committee was not convinced that the evidence is sufficiently robust for it to be recommended. In the NMA, the credible interval surrounding the point estimate for sodium bicarbonate (oral) with oral fluids was very wide, and there was only a single trial arm (comprising 21 participants) contributing to the evidence base (see The committee's discussion of the evidence). We therefore presented results with this intervention excluded.

When we remove sodium bicarbonate + oral fluids from the decision-making space, oral fluids becomes the cheapest intervention. In an incremental analysis, the only intervention that is not dominated by oral fluids is sodium chloride 0.9% (IV) + sodium bicarbonate (IV), with a very high ICER of £510,922 per QALY gained.

Table 30: Deterministic cost-effectiveness results, without sodium bicarbonate + oral fluids

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	Costs (£)	
oral fluids	£21,489	6.347				5.273
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£22,147	6.349	£658	0.0013	£510,922	5.241
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£22,164	6.344	£17	-0.0044	dominated	5.236
NAC (IV bolus) + sodium chloride 0.9% (IV)	£22,190	6.341	£44	-0.0076	dominated	5.232
no (intravenous) hydration	£22,334	6.270	£187	-0.079	dominated	5.153
NAC (oral) + sodium chloride 0.45% (IV)	£22,340	6.330	£193	-0.019	dominated	5.213
sodium bicarbonate (IV)	£22,347	6.329	£200	-0.020	dominated	5.212
NAC (IV) + sodium chloride 0.45% (IV)	£22,363	6.327	£216	-0.022	dominated	5.209
NAC (oral) + sodium chloride 0.9% (IV)	£22,367	6.325	£220	-0.024	dominated	5.207
NAC (oral)	£22,390	6.265	£243	-0.084	dominated	5.146
NAC (oral) + sodium bicarbonate (IV)	£22,478	6.318	£331	-0.031	dominated	5.194
NAC (IV) + sodium chloride 0.9% (IV)	£22,496	6.313	£349	-0.036	dominated	5.188
sodium citrate (oral)	£22,518	6.253	£371	-0.096	dominated	5.127
sodium chloride 0.9% (IV)	£22,563	6.306	£416	-0.042	dominated	5.178
sodium chloride 0.45% (IV)	£23,337	6.236	£1,190	-0.112	dominated	5.070
sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£23,842	6.193	£1,696	-0.156	dominated	5.001

Figure 13 presents the cost-effectiveness plane for these results. The steep gradient of the red line between intervention 10 (oral fluids) and intervention 15 (sodium chloride 0.9% [IV] + sodium bicarbonate [IV]) represents the ICER of £510,922 per QALY gained. All other interventions remain dominated.

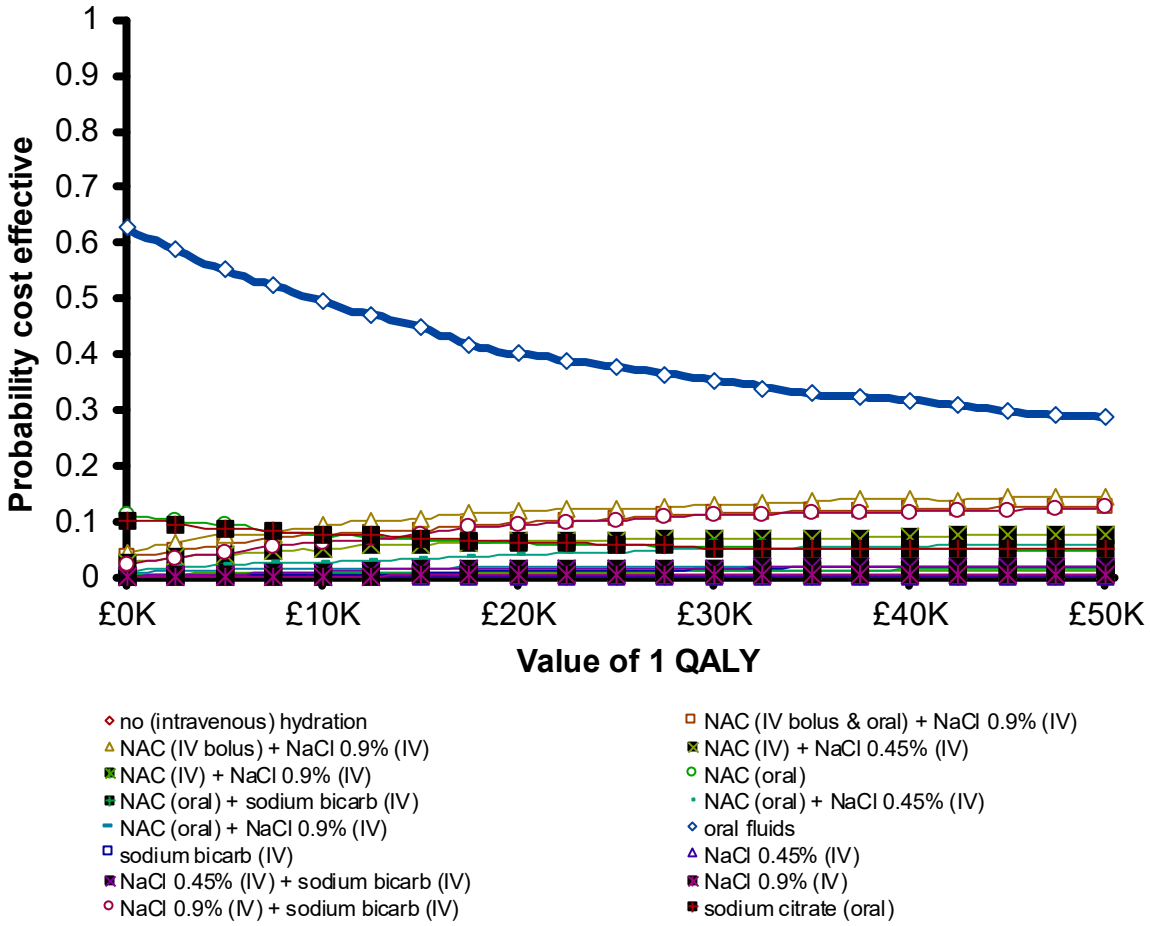


(1) no (intravenous) hydration
(2) NAC (IV bolus & oral) + sodium chloride 0.9% (IV)
(3) NAC (IV bolus) + sodium chloride 0.9% (IV)
(4) NAC (IV) + sodium chloride 0.45% (IV)
(5) NAC (IV) + sodium chloride 0.9% (IV)
(6) NAC (oral)
(7) NAC (oral) + sodium bicarbonate (IV)
(8) NAC (oral) + sodium chloride 0.45% (IV)
(9) NAC (oral) + sodium chloride 0.9% (IV)
(10) oral fluids
(11) sodium bicarbonate (IV)
(12) sodium chloride 0.45% (IV)
(13) sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
(14) sodium chloride 0.9% (IV)
(15) sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
(16) sodium citrate (oral)

Red continuous line indicates cost effectiveness frontier
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY

Figure 13: Cost-effectiveness plane, without sodium bicarbonate + oral fluids

Figure 14 presents the CEAC without sodium bicarbonate + oral fluids. It is evident that oral fluids have the highest probability of being cost-effective and the highest expected net benefit across all values of a QALY. The probability that any of the individual intravenous regimens is best is spread thinly among several possible strategies; however, it can be seen to rise somewhat as increasing value is placed on QALY gains.



Bold line indicates cost-effectiveness acceptability frontier

Figure 14: Cost-effectiveness acceptability curve, without sodium bicarbonate + oral fluids

We conducted an additional PSA in which we group the interventions according to whether they are oral fluids, contain sodium chloride 0.9% and/or sodium bicarbonate, or are something else (e.g. sodium chloride 0.45%, sodium citrate, NAC alone or no treatment). Figure 15 shows that oral fluids have the highest probability of being cost effective when a QALY is valued at less than approximately £25,000, above which regimens containing IV sodium chloride 0.9% and/or sodium bicarbonate are most likely to be cost effective.

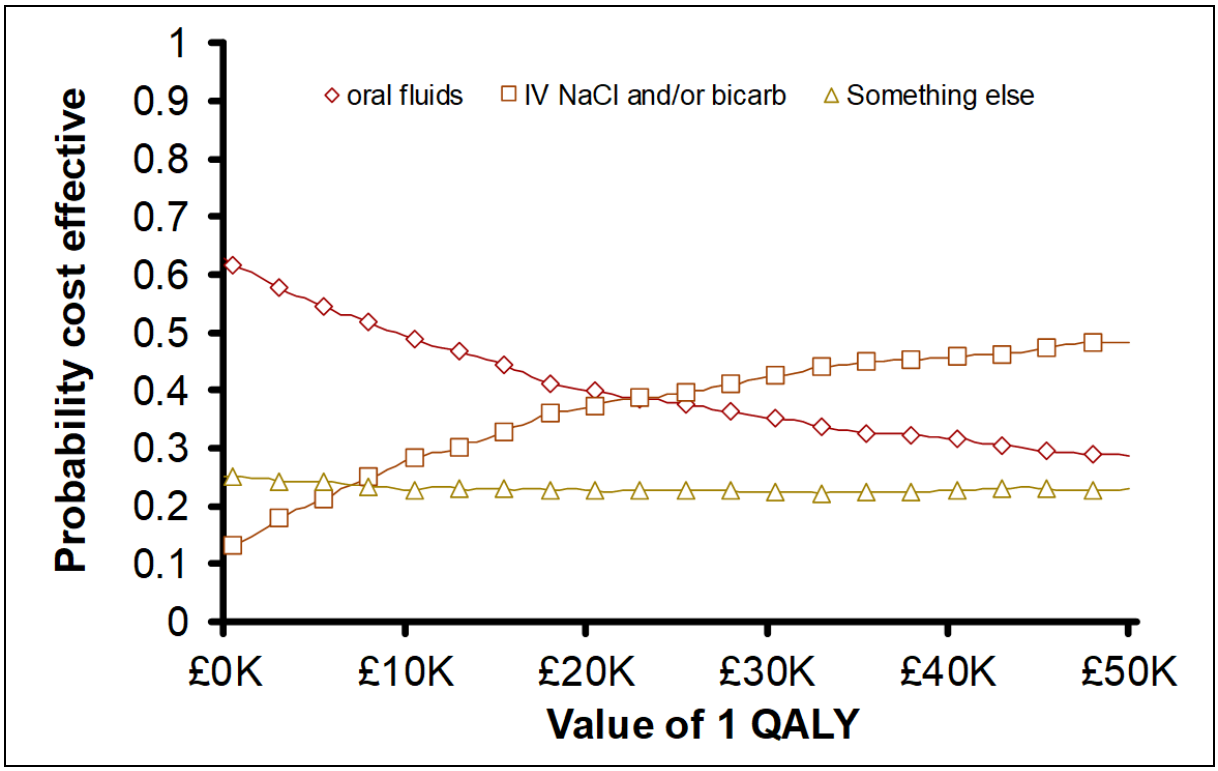
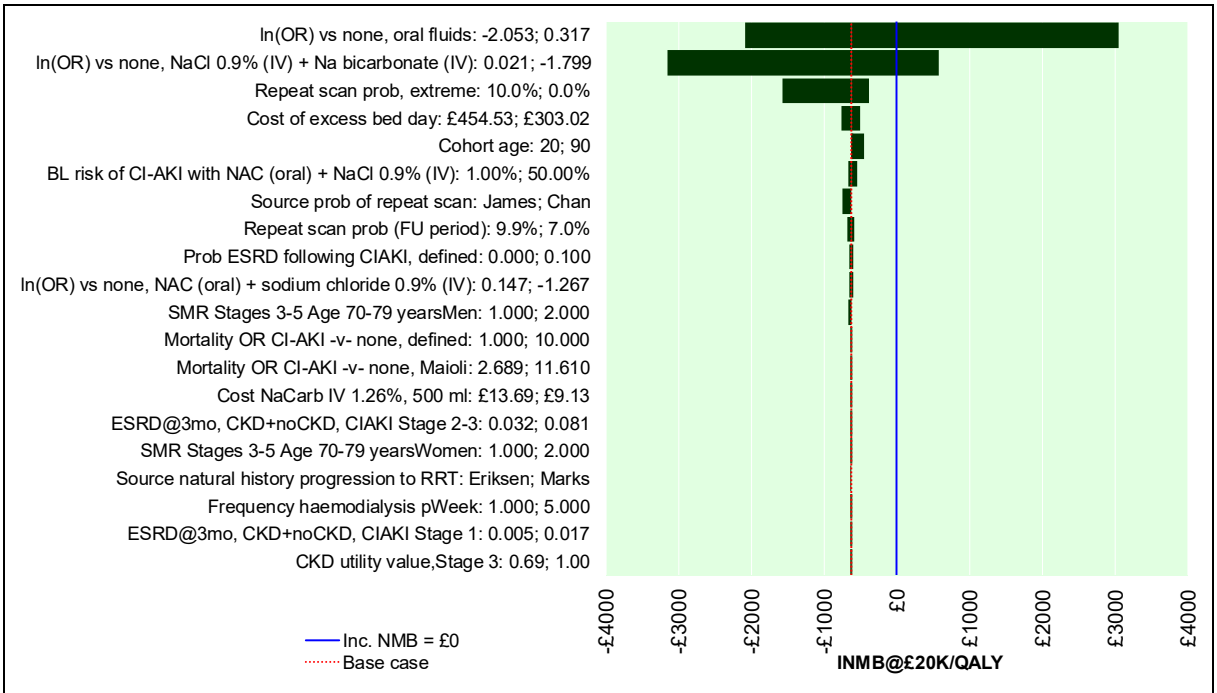


Figure 15: Cost-effectiveness acceptability curve, without sodium bicarbonate + oral fluids, grouped regimens

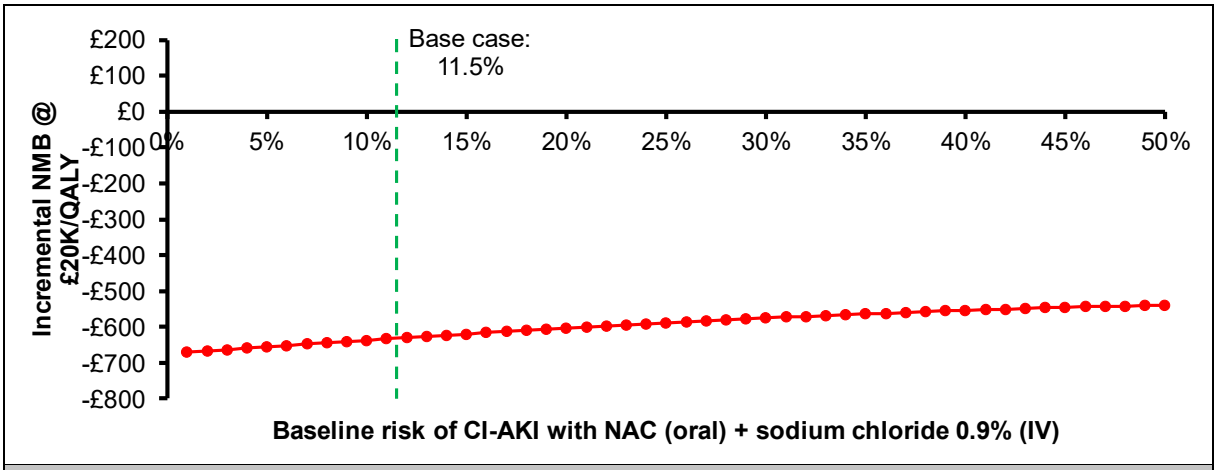
We also undertook an OSA for this scenario, in which we compared sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids (Figure 16). Again, the only parameters that have the potential to alter the cost-effectiveness conclusion are the relative treatment effects; the incremental net monetary benefit becomes positive (that is, the intravenous regimen becomes cost effective) when oral fluids are assumed to be less effective, and when sodium chloride 0.9% (IV) + sodium bicarbonate (IV) is assumed to be more effective.



INMB = incremental net monetary benefit
20 most influential parameters shown

Figure 16: One-way sensitivity analysis without sodium bicarbonate + oral fluids **– sodium chloride 0.9% (IV) + sodium bicarbonate (IV)**

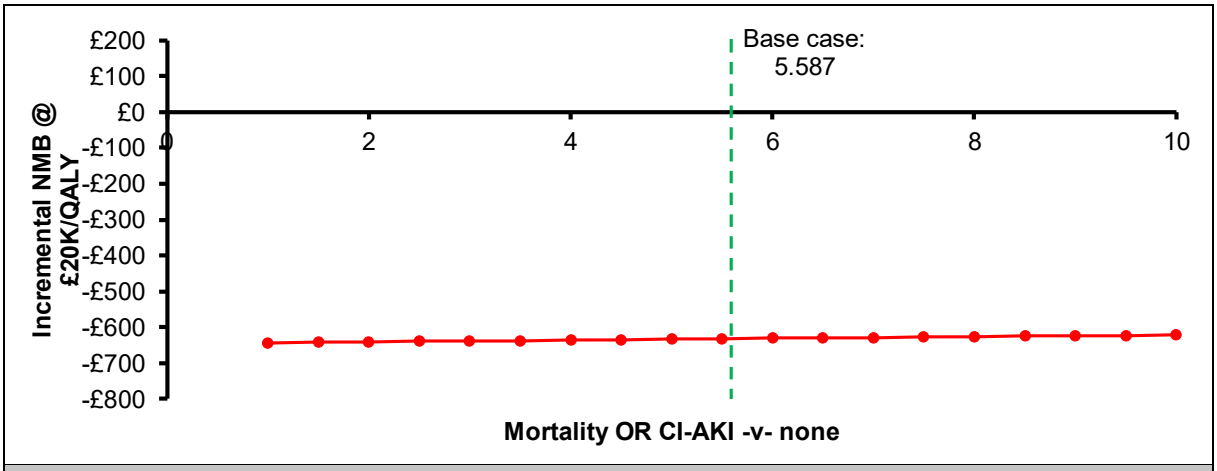
To further explore the effects of the baseline risk of CI-AKI on the ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids, we varied the baseline risk between extreme values (1% and 50%; base case 11.5%) in a threshold analysis (Figure 17). No value of the baseline risk of CI-AKI leads to a positive incremental net monetary benefit (INMB); therefore, when all other parameters are evaluated at their base-case value, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) is unlikely to be cost-effective compared with oral fluids at any plausible baseline risk of CI-AKI if a QALY is valued at £20,000.



NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 17: Threshold analysis – baseline risk of CI-AKI, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

In an additional threshold analysis, we vary the mortality OR for CI-AKI versus no CI-AKI between extreme values (1 and 10; base case 5.59) to determine the effect on the ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids (Figure 18). The INMB remains negative across all values of the OR, indicating that no plausible value of this parameter leads to sodium chloride 0.9% (IV) + sodium bicarbonate (IV) becoming cost effective if QALYs are valued at £20,000 each.

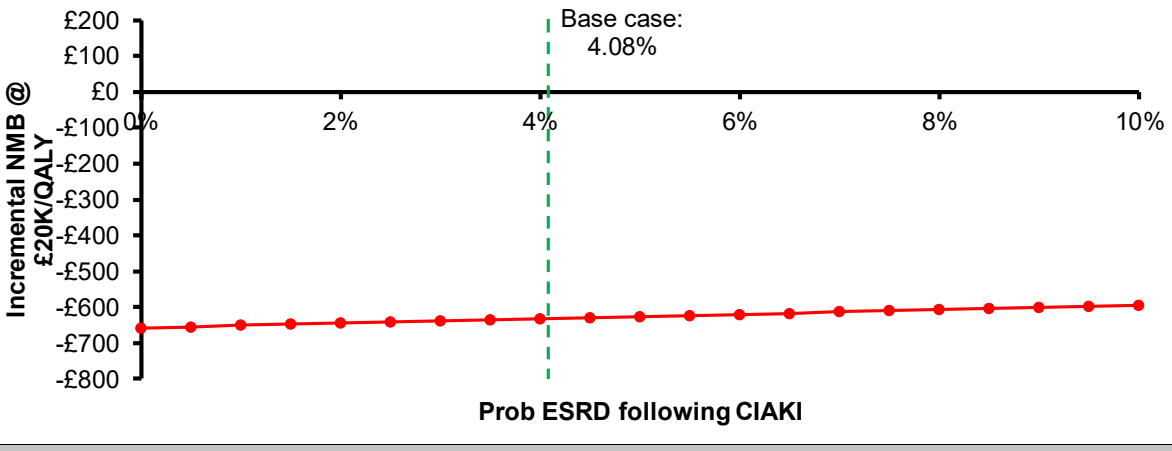


NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 18: Threshold analysis – mortality odds ratio for CI-AKI vs no CI-AKI, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

To determine whether the risk of ESRD following an episode of CI-AKI has the potential to meaningfully affect the ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus

oral fluids, we varied this parameter between extreme values (0% and 10%; base case 4.1%). No value of this parameter leads to a positive INMB (Figure 19).



NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 19: Results – threshold analysis, probability of ESRD following CI-AKI, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

Emergency setting

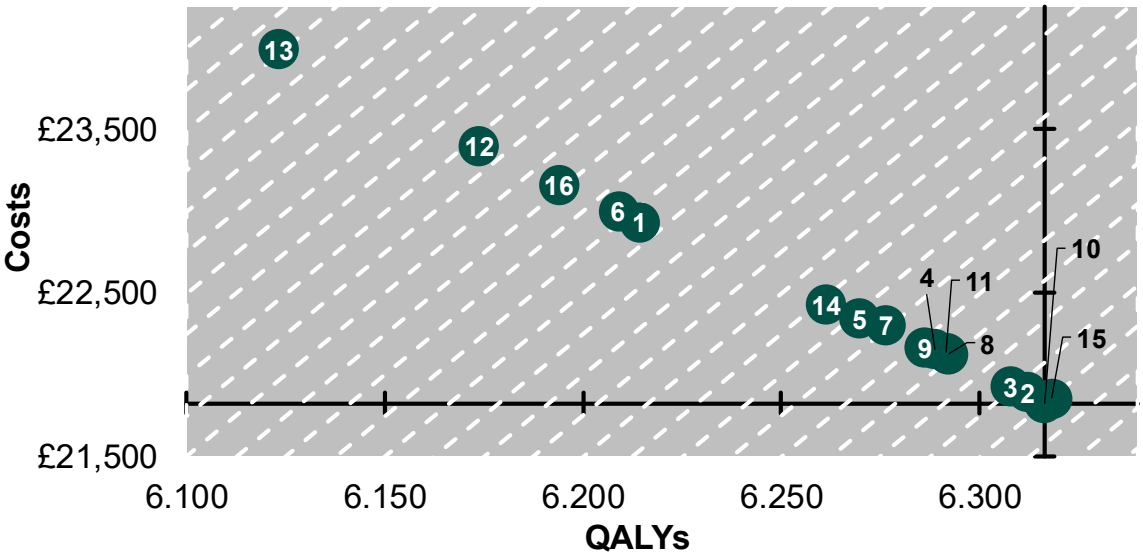
We undertook a scenario analysis for the emergency population (see Methods: Deterministic sensitivity analysis), in which we use the baseline risk of CI-AKI obtained from a synthesis of trials from the emergency setting, and assume that everyone is already an inpatient, so no excess bed day costs are applied for any intervention. We conducted this analysis without sodium bicarbonate + oral fluids, as the committee did not deem this intervention to be an option for recommendation due to the wide credible intervals surrounding the effect point estimate and the small evidence base upon which the the point estimate is based; excluding it from the analysis allowed the committee to better interpret results for the remaining interventions.

Table 31 presents deterministic cost–utility results for the emergency setting. Oral fluids remain the cheapest option; however, in this emergency scenario, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) now has an ICER of £16,112 compared with oral fluids. The differences between these strategies are very small: a QALY gain of 0.0018 is equivalent to around an extra two-thirds of a day in perfect health over an average patient's lifetime. All other interventions remain dominated. Note that when the 2 emergency assumptions are applied individually, the ICER remains greater than £20,000 per QALY (£26,410 per QALY when the inpatient bed day assumption is applied, and £366,769 per QALY when the emergency baseline risk of CI-AKI is applied).

Table 31: Results – deterministic cost-effectiveness results, emergency setting, without sodium bicarbonate + oral fluids

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	Costs (£)	
oral fluids	£21,824	6.317				5.225
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£21,853	6.318	£29	0.0018	£16,112	5.226
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£21,888	6.312	£36	-0.0060	dominated	5.218
NAC (IV bolus) + sodium chloride 0.9% (IV)	£21,928	6.308	£75	-0.0104	dominated	5.211
NAC (oral) + sodium chloride 0.45% (IV)	£22,122	6.292	£269	-0.026	dominated	5.186
sodium bicarbonate (IV)	£22,131	6.292	£278	-0.027	dominated	5.185
NAC (IV) + sodium chloride 0.45% (IV)	£22,155	6.289	£302	-0.030	dominated	5.181
NAC (oral) + sodium chloride 0.9% (IV)	£22,166	6.286	£313	-0.032	dominated	5.178
NAC (oral) + sodium bicarbonate (IV)	£22,304	6.277	£451	-0.042	dominated	5.161
NAC (IV) + sodium chloride 0.9% (IV)	£22,341	6.270	£488	-0.049	dominated	5.153
sodium chloride 0.9% (IV)	£22,429	6.261	£576	-0.057	dominated	5.140
no (intravenous) hydration	£22,933	6.214	£1,080	-0.104	dominated	5.068
NAC (oral)	£23,001	6.209	£1,148	-0.109	dominated	5.059
sodium citrate (oral)	£23,160	6.194	£1,307	-0.124	dominated	5.036
sodium chloride 0.45% (IV)	£23,400	6.174	£1,547	-0.144	dominated	5.004
sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£23,988	6.123	£2,135	-0.195	dominated	4.924

Figure 20 presents the cost-effectiveness plane for these results. The points representing oral fluids (number 10) and sodium chloride 0.9% (IV) + sodium bicarbonate (IV) are very close together, which is indicative of the small incremental cost and QALY differences between these 2 interventions.

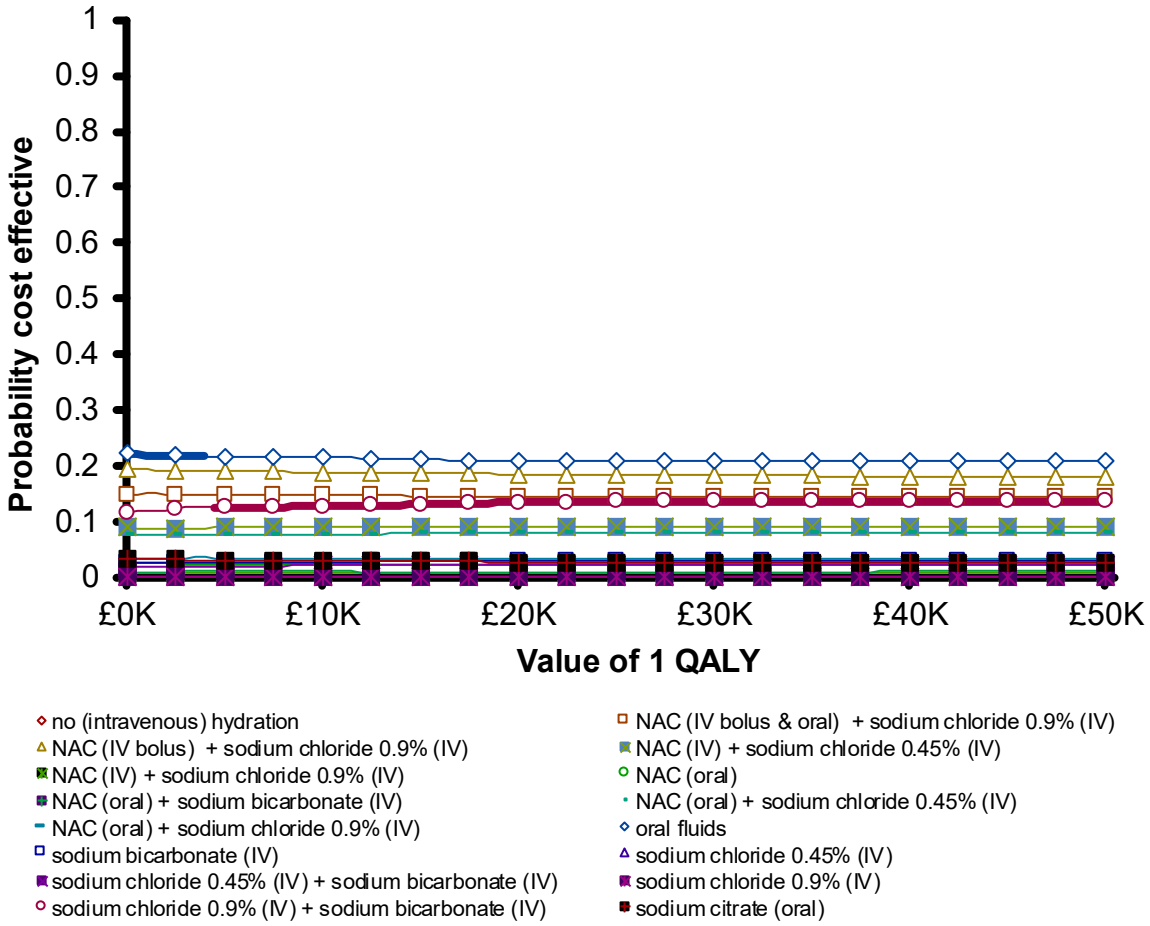


(1) no (intravenous) hydration
(2) NAC (IV bolus & oral) + sodium chloride 0.9% (IV)
(3) NAC (IV bolus) + sodium chloride 0.9% (IV)
(4) NAC (IV) + sodium chloride 0.45% (IV)
(5) NAC (IV) + sodium chloride 0.9% (IV)
(6) NAC (oral)
(7) NAC (oral) + sodium bicarbonate (IV)
(8) NAC (oral) + sodium chloride 0.45% (IV)
(9) NAC (oral) + sodium chloride 0.9% (IV)
(10) oral fluids
(11) sodium bicarbonate (IV)
(12) sodium chloride 0.45% (IV)
(13) sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
(14) sodium chloride 0.9% (IV)
(15) sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
(16) sodium citrate (oral)

Red continuous line indicates cost effectiveness frontier
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY

Figure 20: Results – cost-effectiveness plane, emergency setting, without sodium bicarbonate + oral fluids

Figure 21 shows the CEAC. It is evident that, regardless of the value ascribed to QALYs, none of the individual modelled strategies can be identified as optimal with any degree of confidence. Oral fluids appear to have the highest probability of being cost effective, but sodium chloride 0.9% (IV) + sodium bicarbonate (IV) has the greatest expected net benefit if a QALY is valued at £20,000 (Table 31). Oral fluids have the greatest expected net benefit at low QALY values (below approximately £4,000).



Bold line indicates cost-effectiveness acceptability frontier

Figure 21: Results – CEAC, emergency setting, without sodium bicarbonate + oral fluids

The CEAC for grouped interventions in the emergency setting shows that at all QALY values, regimens containing sodium chloride 0.9% and/or sodium bicarbonate have the highest probability of being cost effective (Figure 22).

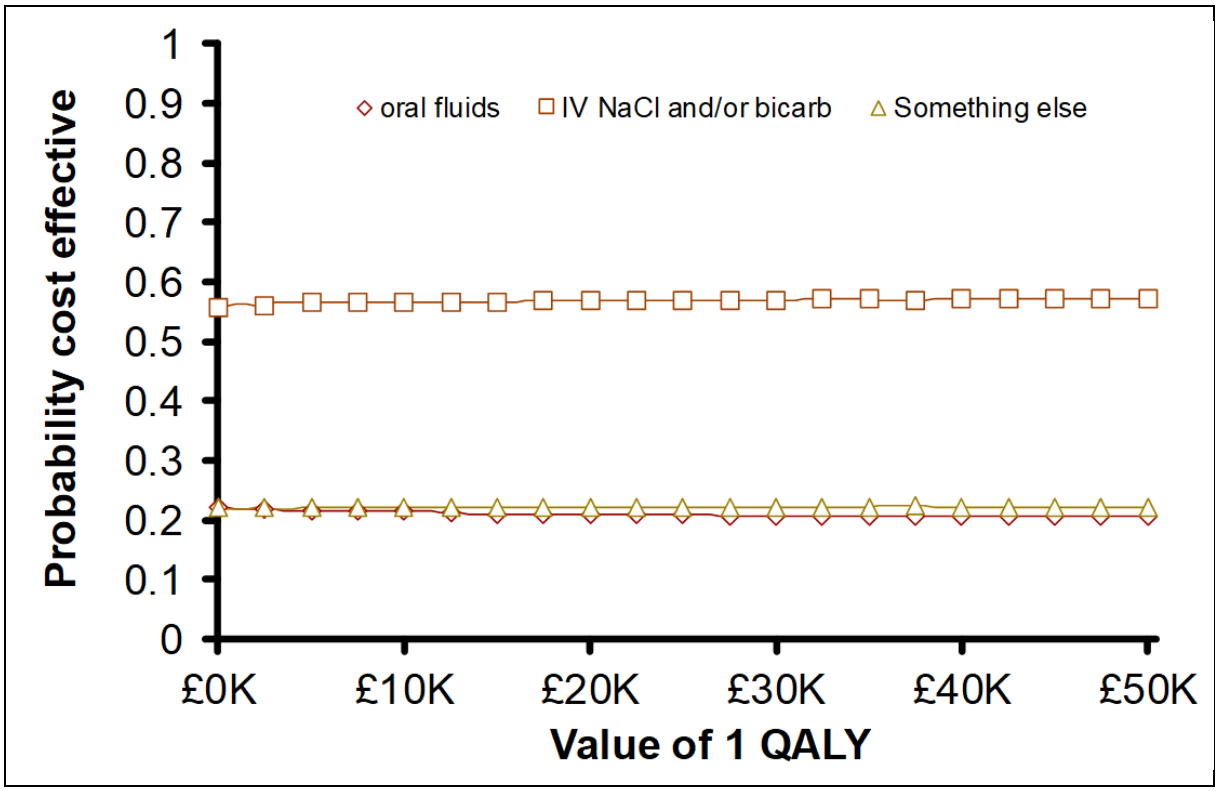
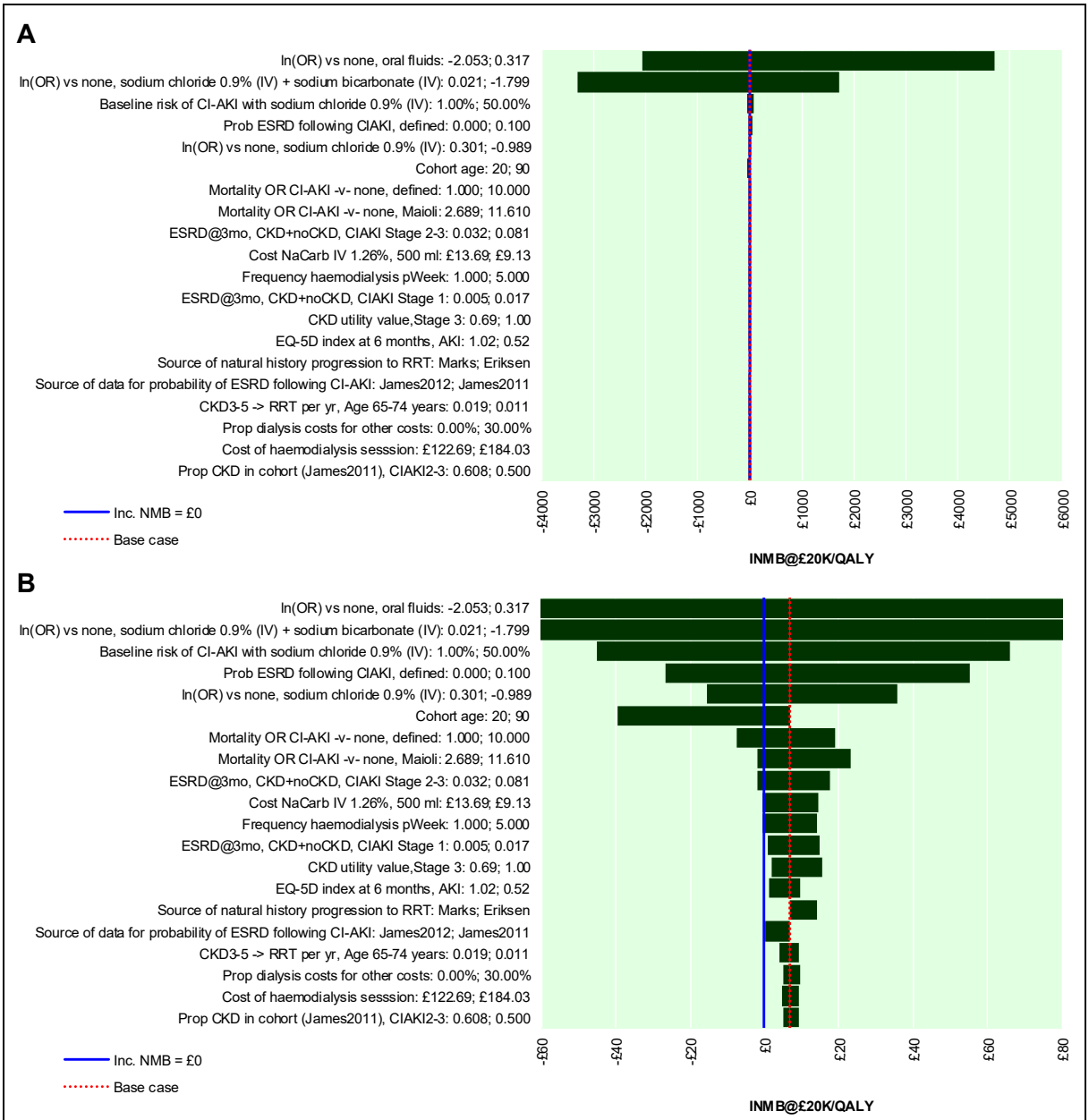


Figure 22: Cost-effectiveness acceptability curve, without sodium bicarbonate + oral fluids, grouped regimens – emergency

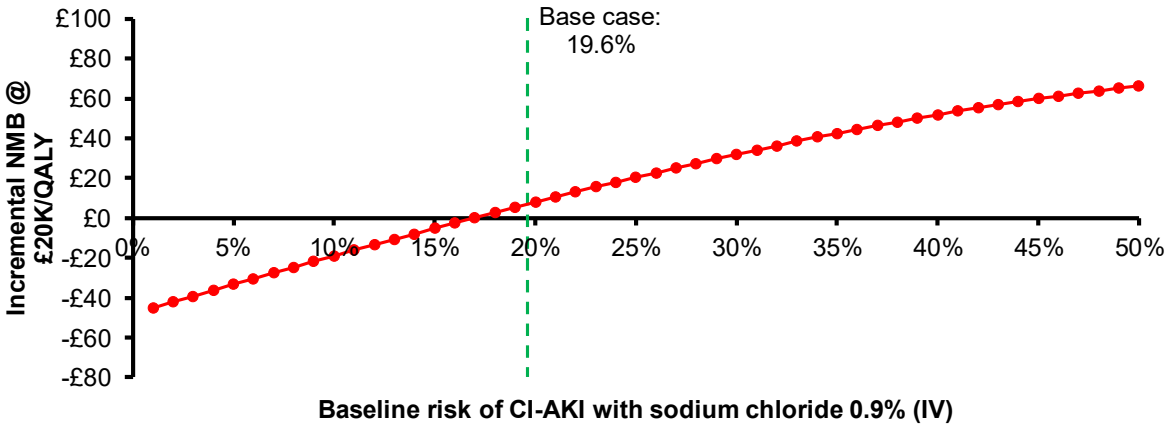
We undertook an OSA for this scenario (Figure 23), in which we compare sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids. The uncertainty surrounding the cost-effectiveness of sodium chloride 0.9% (IV) + sodium bicarbonate (IV) in this scenario is evidenced by the base case (red dotted line) overlapping with the line indicating an incremental net monetary benefit of £0. Changes to the relative treatment effects (top 2 parameters) have a large effect on results; however, even those parameters that make very little difference to results in absolute terms would still have the potential to change the cost-effectiveness conclusion if a decision-maker were to adopt a rigid threshold of £20,000/QALY.



INMB = incremental net monetary benefit
20 most influential parameters shown; panel B shows same data as panel A, but 'zoomed in' to a much narrower range on the x-axis

Figure 23: Results – OSA, emergency setting, without sodium bicarbonate + oral fluids

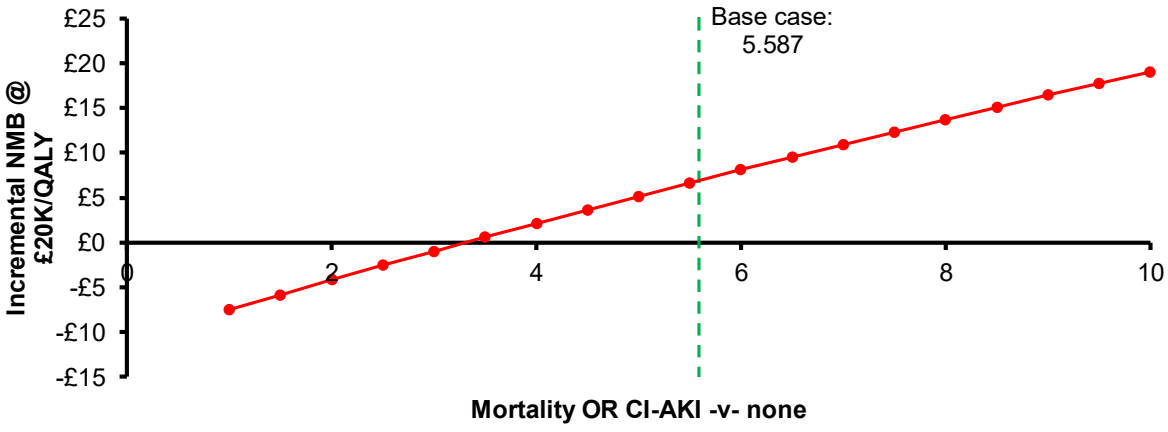
We repeated the same 3 threshold analyses in the emergency population to compare sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids. When the baseline risk of CI-AKI was varied between extreme values (1% and 50%; base case 19.6%) the INMB becomes negative at risk values of around 17% and below, indicating that the ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids exceeds £20,000 per QALY gained at these values (Figure 24). Notably, the 95% confidence interval for the baseline risk of CI-AKI in the emergency population is 10.6% to 33.4%, therefore the INMB becomes negative within the plausible boundaries for this parameter.



NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 24: Threshold analysis – baseline risk of CI-AKI, emergency population, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

When varying the mortality OR for CI-AKI versus no CI-AKI between extreme values (1 and 10; base case 5.59) to determine the effect on the ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids (Figure 25), the INMB becomes negative at OR values of around 3.25 or less, which is within the 95% confidence interval of the mortality OR (2.69 to 11.61).

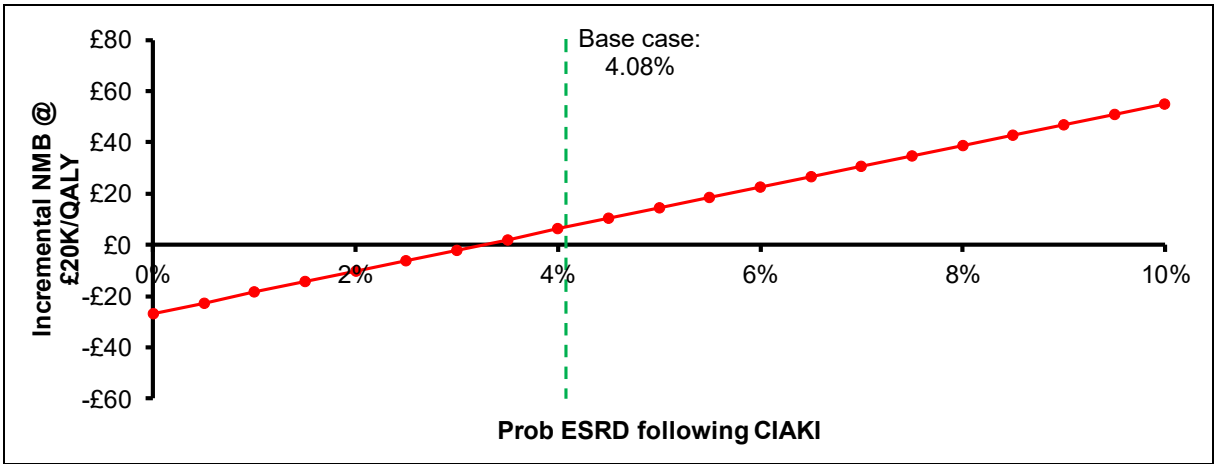


NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 25: Threshold analysis – mortality odds ratio for CI-AKI vs no CI-AKI, emergency population, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

We varied the risk of ESRD following an episode of CI-AKI in the emergency population to determine whether it has the potential to meaningfully affect the ICER for sodium chloride

0.9% (IV) + sodium bicarbonate (IV) versus oral fluids (Figure 26). We varied this parameter between extreme values (0% and 10%; base case 4.1%). Probabilities of approximately 3.25% and below result in a negative INMB.



NMB = incremental net monetary benefit
Values greater than 0 indicate sodium chloride 0.9% (IV) + sodium bicarbonate (IV) would be associated with an ICER better than £20,000/QALY compared with oral fluids

Figure 26: Threshold analysis – probability of ESRD following CI-AKI, emergency population, sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids

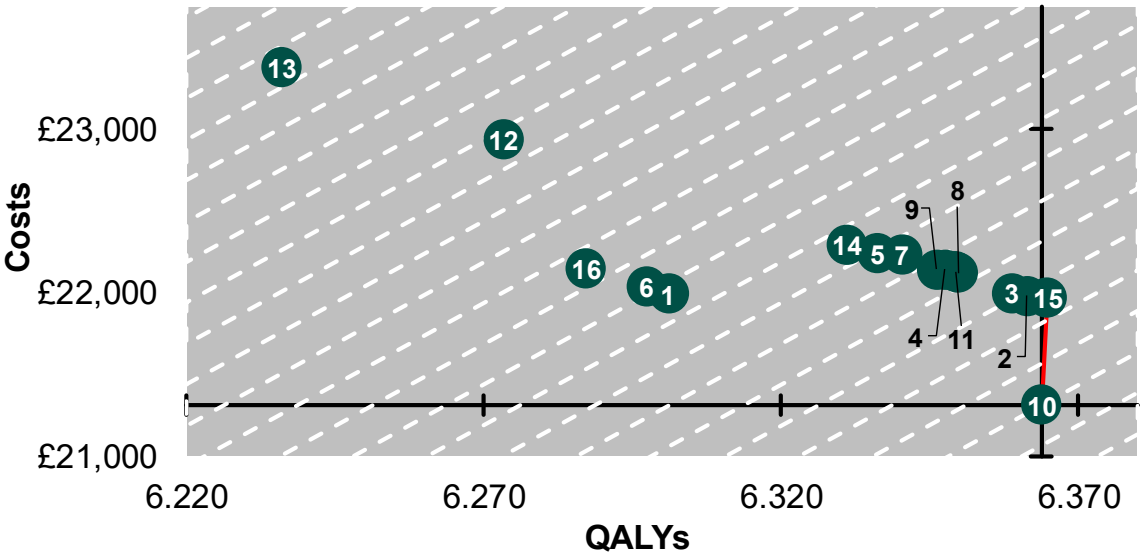
Elective setting

We undertook a scenario analysis in which we assume that all patients are undergoing elective procedures. This involves using the synthesised baseline risk of CI-AKI from elective trials only (see Table 19), and the same assumptions surrounding excess bed day costs as the base-case analysis. This represents a population at comparatively low risk of CI-AKI. Base case cost–utility results are presented in Table 32. Compared with the base case ICER of £510,922 per QALY gained, the ICER increases to £655,323 per QALY gained in the elective population. All other interventions are dominated by oral fluids.

Table 32: Results – deterministic cost-effectiveness results, elective setting, without sodium bicarbonate + oral fluids

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	Costs (£)	
oral fluids	£21,312	6.364				5.298
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£21,974	6.365	£661	0.0010	£655,323	5.266
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£21,981	6.361	£7	-0.0034	dominated	5.262
no (intravenous) hydration	£21,992	6.301	£18	-0.0638	dominated	5.201
NAC (IV bolus) + sodium chloride 0.9% (IV)	£22,000	6.359	£26	-0.006	dominated	5.259
NAC (oral)	£22,040	6.297	£66	-0.067	dominated	5.195
NAC (oral) + sodium chloride 0.45% (IV)	£22,123	6.350	£149	-0.015	dominated	5.244
sodium bicarbonate (IV)	£22,129	6.349	£156	-0.015	dominated	5.243
NAC (IV) + sodium chloride 0.45% (IV)	£22,140	6.348	£167	-0.017	dominated	5.241
NAC (oral) + sodium chloride 0.9% (IV)	£22,141	6.346	£167	-0.019	dominated	5.239
sodium citrate (oral)	£22,146	6.287	£172	-0.078	dominated	5.180
NAC (oral) + sodium bicarbonate (IV)	£22,236	6.340	£262	-0.024	dominated	5.229
NAC (IV) + sodium chloride 0.9% (IV)	£22,243	6.336	£269	-0.029	dominated	5.224
sodium chloride 0.9% (IV)	£22,296	6.331	£322	-0.034	dominated	5.216
sodium chloride 0.45% (IV)	£22,939	6.273	£965	-0.092	dominated	5.126
sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£23,379	6.236	£1,405	-0.129	dominated	5.067

Figure 27 plots these results on the cost-effectiveness plane. As for the base case, the extremely steep gradient of the red line represents the very high ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids.

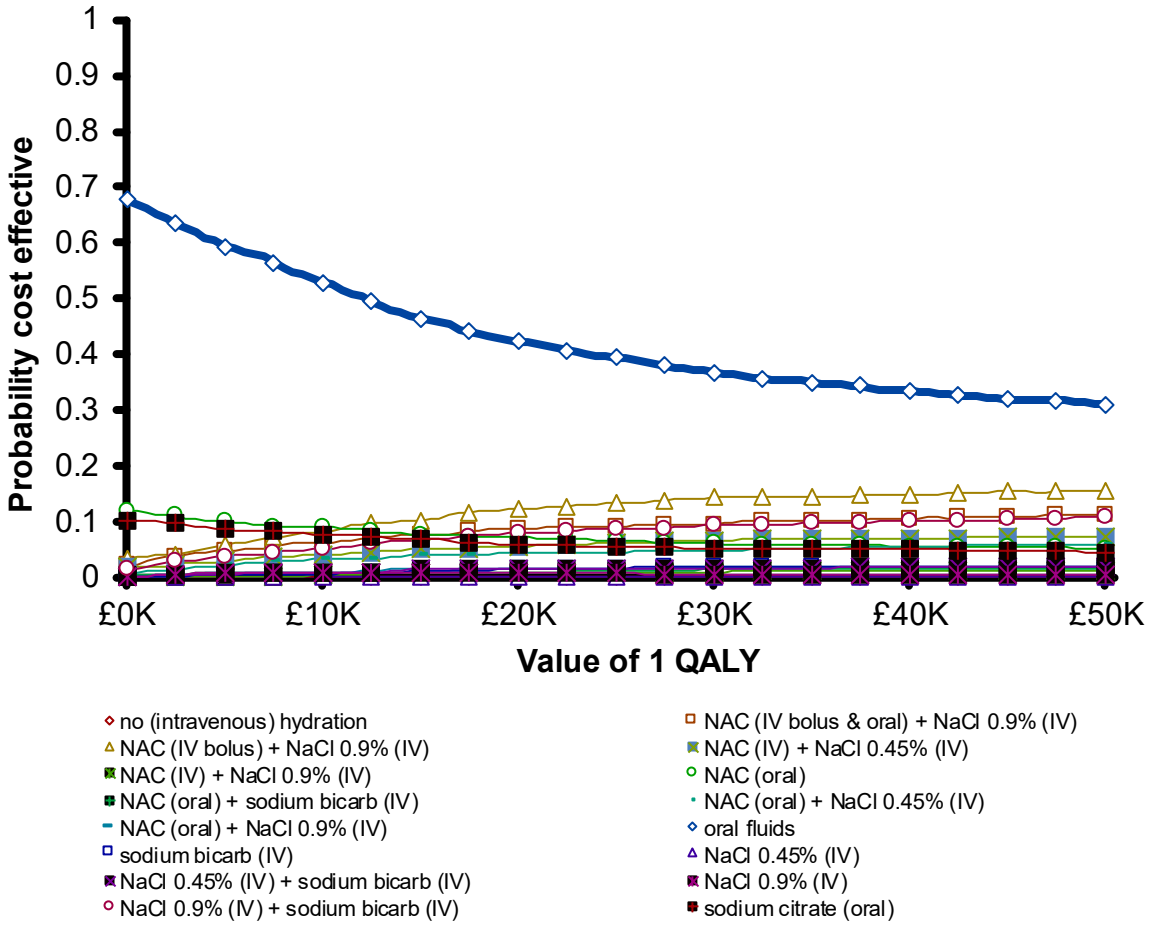


(1) no (intravenous) hydration
(2) NAC (IV bolus & oral) + sodium chloride 0.9% (IV)
(3) NAC (IV bolus) + sodium chloride 0.9% (IV)
(4) NAC (IV) + sodium chloride 0.45% (IV)
(5) NAC (IV) + sodium chloride 0.9% (IV)
(6) NAC (oral)
(7) NAC (oral) + sodium bicarbonate (IV)
(8) NAC (oral) + sodium chloride 0.45% (IV)
(9) NAC (oral) + sodium chloride 0.9% (IV)
(10) oral fluids
(11) sodium bicarbonate (IV)
(12) sodium chloride 0.45% (IV)
(13) sodium chloride 0.45% (IV) + sodium bicarbonate (IV)
(14) sodium chloride 0.9% (IV)
(15) sodium chloride 0.9% (IV) + sodium bicarbonate (IV)
(16) sodium citrate (oral)

Red continuous line indicates cost effectiveness frontier
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY

Figure 27: Cost-effectiveness plane, elective setting, without sodium bicarbonate + oral fluids

Figure 28 presents the CEAC. Results are similar to the base case in that oral fluids have the highest probability of cost effectiveness and have the highest expected net benefit across all QALY values.



Bold line indicates cost-effectiveness acceptability frontier

Figure 28: Results – CEAC, elective setting, without sodium bicarbonate + oral fluids

The CEAC for the grouped regimens in the elective setting (Figure 29) is similar to the equivalent figure when elective and emergency are grouped (Figure 15), although the QALY value at which a sodium chloride 0.9% and/or sodium bicarbonate regimen overtakes oral fluids is higher in the elective setting (at approximately £27,000 per QALY).

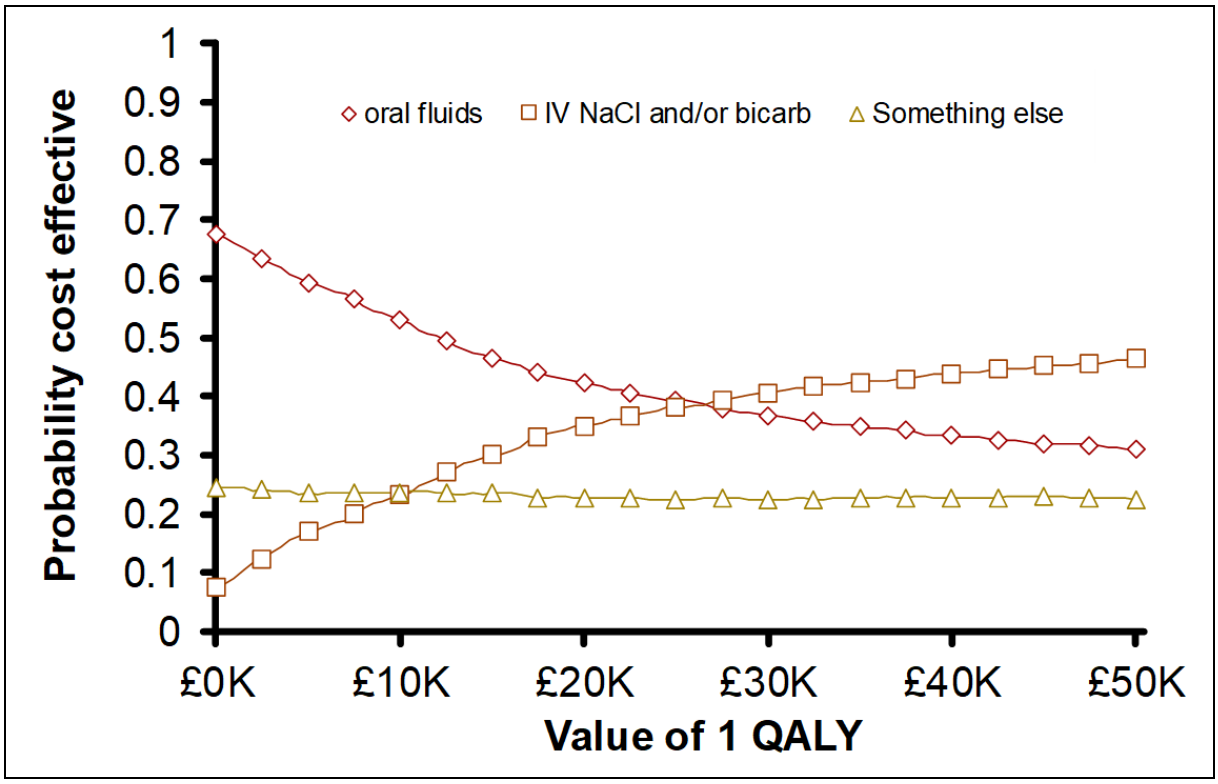
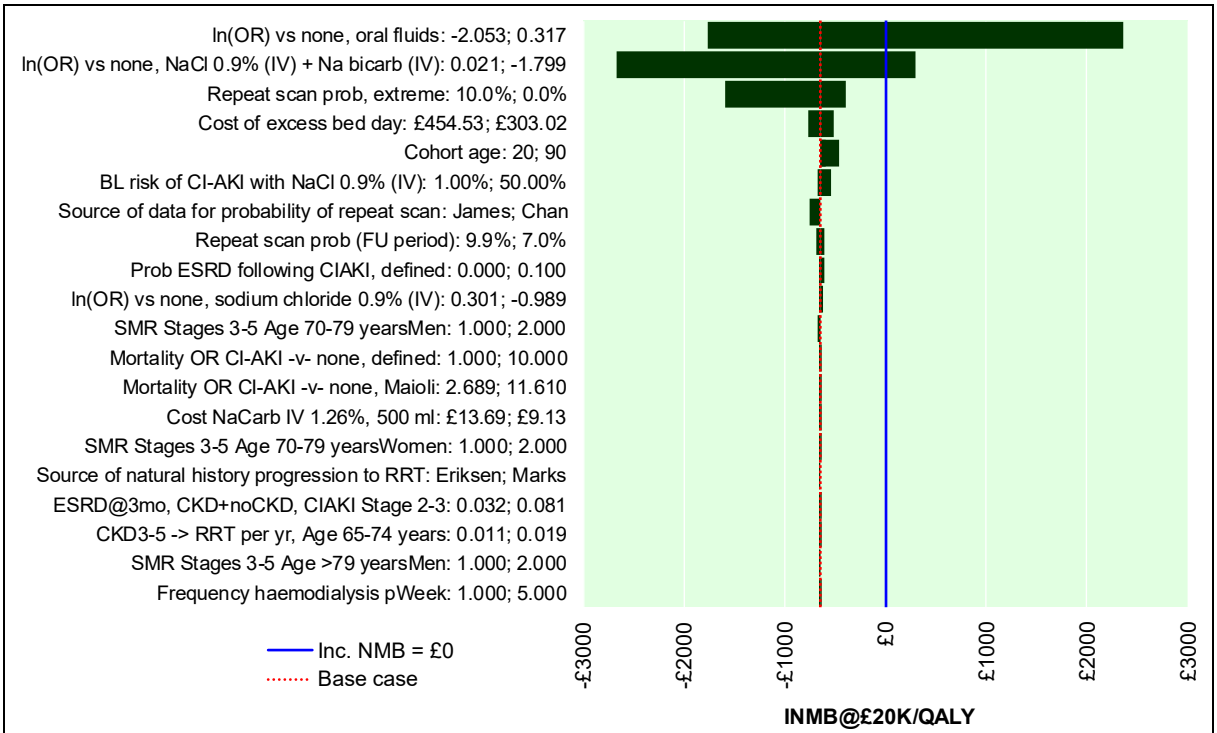


Figure 29: Cost-effectiveness acceptability curve, without sodium bicarbonate + oral fluids, grouped regimens – elective

We also undertook an OSA for this scenario (Figure 30). Results are very similar to the analysis conducted for the base case without sodium bicarbonate (oral) + oral fluids removed (Figure 30), with only the relative treatment effects for oral fluids alone, or sodium chloride 0.9% (IV) + sodium bicarbonate (IV) having the potential to result in a positive incremental net monetary benefit.



INMB = incremental net monetary benefit
20 most influential parameters shown

Figure 30: Results – OSA, elective setting, without sodium bicarbonate + oral fluids

Discussion

Principal findings

The aim of the current analysis was to answer the research question 'What is the comparative clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults?'. To answer this question, we modelled a population with an average age of 70 years who have CKD Stages 3–5 (pre-RRT) and are at risk of CI-AKI from PCI procedures, using the results of the clinical NMA to inform the relative treatment effects for the different interventions.

In the base-case analysis, sodium bicarbonate (oral) plus oral fluids dominates all other interventions. Other than the effectiveness of the intervention (which is extremely uncertain), none of the parameters varied in sensitivity analyses change this result. Notably, the model results directly reflect results of the NMA, indicating that the probability of CI-AKI is the key parameter driving model results. When sodium bicarbonate (oral) plus oral fluids is removed from the decision space, oral fluids alone become the most cost-effective intervention. The only intervention not dominated by oral fluids is sodium chloride 0.9% (IV) + sodium bicarbonate (IV), with a base-case ICER of £510,922 per QALY gained. We conducted scenario analyses in emergency and elective populations with sodium bicarbonate (oral) plus oral fluids removed from the decision space. The ICER for sodium chloride 0.9% (IV) + sodium bicarbonate (IV) versus oral fluids increased further in the elective population to £655,323 per QALY gained; however, it dropped to £16,112 per QALY gained in the emergency population. All other interventions remain dominated in all scenarios.

We conducted an additional analysis separating results from the 17 strategies down into a simple 3-way split: (i) oral fluids alone, (ii) intravenous regimens with sodium chloride 0.9% and/or sodium bicarbonate (as currently recommended), (iii) other options (including oral NAC alone, no hydration regimen and IV sodium chloride 0.45%). Probabilistic results suggest that there is about a 60% chance that 1 or other of the simulated regimens containing intravenous sodium chloride 0.9% and/or intravenous sodium bicarbonate provides best value in the emergency setting (if a QALY is valued at £20,000). Oral fluids alone have the highest probability of being cost-effective at £20,000 per QALY in the grouped (emergency plus elective) and elective only subgroups.

Strengths of the analysis

Although this was an update of an existing model, we have made various changes and additions to use the most recent data available to us and refine the clinical pathway in line with the committee's advice. As an example, the previous model did not incorporate the costs and QoL of kidney transplantation within the CKD stage 5 state, while we felt it was an important component and therefore included it within the updated model. We were also able to find multiple more recent or more appropriate sources of data for model parameterisation. For example, we obtained the risk of ESRD following CI-AKI from a study in people with CKD specifically (Chan et al., 2015), and we obtained the mortality relative risks for the RRT state from the UK Renal Registry (UK Renal Registry, 2018).

A key strength of the analysis is that it relies on an NMA for estimates of the relative treatment effects. To our knowledge, this is the most up-to-date estimate of the treatment effects for the included interventions. Furthermore, although the base-case results of the model directly reflect the results of the NMA, we synthesised a wealth of additional types of data from various sources to help the committee make informed recommendations that were not solely based on clinical effectiveness. As part of this, we presented long-term clinical outcomes over patients' lifetimes to the committee, such as life-years and rates of ESRD.

The analyses presented here also benefit from extensive one-way and scenario analyses, as well as a PSA. All parameters and key scenarios were included in univariable analyses, and we explored key inputs in greater detail, including the use of alternative data sources. These were subject to different scenarios and threshold analyses. In particular, our modelling of emergency and elective subgroups showed the potential for important distinctions in cost–utility outcomes. In the emergency scenario, we were able to show how the balance of costs and benefits changes at different baseline risks of CI-AKI.

Lastly, the model was updated in close collaboration with the expert guideline committee. As part of this, the committee had several opportunities to review and discuss the model structure and inputs. This ensured the model had a high degree of external validity and was an appropriate representation of the true clinical pathway in CI-AKI.

Limitations of the analysis

Although we aimed to match the population from the clinical review as closely as possible, it was necessary to make some simplifying assumptions that meant there were some deviations from the original PICO in terms of clinical characteristics. For example, we only looked at people with stages 3–5 CKD (pre-dialysis) to represent those 'at risk' of CI-AKI, while the clinical review used a broader definition and therefore may have included people with, for example, myocardial infarction. Similarly, we used repeat PCI as a proxy for repeat scans, while the reasons for contrast administration within the clinical review varied.

There were some parameters for which suitable data could not be found. In such cases we asked the committee for their advice or used data sources that were not directly applicable to the population of interest. For example, we were unable to find an appropriate UK study that reports the utility value associated with CI-AKI in people with CKD; therefore, we used data in patients with AKI (from any cause) who were critically ill and only a fraction of whom had CKD (Nisula et al., 2013). An additional example is the number of temporary dialysis sessions required after CI-AKI; this did not appear to be reported in the literature, so we asked the committee for their advice on the number and type of dialysis sessions.

In some cases, we were able to find data, but it did not exactly match our needs or our population of interest. An example of this is mortality in CKD Stages 3–5: the mortality data for stage 3–5 CKD are taken from a cohort of people who have stage 3 CKD at baseline, and therefore may underestimate mortality. The mortality data for RRT, however, are taken from the UK renal registry, which is a good representation of our population of interest. In addition, there were some sources that did not report the data with the appropriate uncertainty estimates for the PSA. An example of this is the version of the NHS reference costs used within the model (2017–18) does not report the lower and upper quartiles for the cost estimates. We therefore assumed costs were fixed, which means uncertainty surrounding the reference costs is not accounted for within the model. Arguably, however, there is no parameter uncertainty attached to NHS reference costs, as they represent all NHS activity, and are, therefore, not subject to sampling error.

There are some attributes of the clinical and disease pathway that we decided not to model to avoid the model becoming overly complex. For example, people who have had an episode of CI-AKI and then recover are still likely to be at an increased risk of mortality and other long-term complications. This has not been incorporated within the model, and as such mortality rates in the Stage 3–5 group may be underestimated as the state will include some people who have had one or more cases of CI-AKI. Similarly, we assume that people who are within the Stage 3–5 state have the same probability of repeat scans, regardless of whether they have previously had an episode of CI-AKI. In clinical practice, it is likely that health professionals will be less likely to recommend scans in people who have had prior CI-AKI, particularly if alternatives are available.

Although a strength of the analysis was our scenario analysis in elective and emergency settings, there were additional subgroups specified in the review protocol that we did not have enough data to explore, for example people with diabetes, sepsis or hypovolaemia. This could be an area for future research.

The model results are based on results of the associated NMA, which has its own limitations that need to be considered when interpreting results of the model. When the model is analysed deterministically, only the point estimates from the NMA are used, which is why sodium bicarbonate (oral) plus oral fluids appears superior to all other options. However, data on the effectiveness of sodium bicarbonate (oral) plus oral fluids are limited and uncertain, and as such the point estimate has an extremely wide credible interval. The committee was aware of this and accounted for it during decision-making.

Comparison with other CUAs

No published cost–utility analyses were found to help answer the review question during the systematic literature search; therefore, there is a lack of clear reference point for this analysis. This was also the case during development of the previous version of the guideline.

Conclusions

In the base-case analysis, sodium bicarbonate (oral) plus oral fluids dominates all other interventions. However, the evidence surrounding the effectiveness of this intervention is extremely uncertain. Upon removal of this intervention from the decision space, oral fluids become the most cost effective; however, this is sensitive to assumptions surrounding the underlying risk of CI-AKI in the population. In patients who are undergoing elective procedures and are therefore at a lower baseline risk of CI-AKI, oral fluids remain the most cost effective. However, for patients undergoing emergency procedures and who are at a higher risk of CI-AKI, sodium chloride 0.9% plus sodium bicarbonate becomes cost-effective. When interventions are grouped, any regimen containing intravenous sodium chloride 0.9% and/or intravenous sodium bicarbonate provides best value in the emergency setting. These results indicate that an IV regimen including sodium chloride 0.9% and/or sodium bicarbonate is cost effective for people who are at a high risk of CI-AKI, while oral fluids may be sufficient for people at a lower risk.

Table of parameters

All parameters used in the model are summarised in Table 33, including details of the distributions and parameters used in probabilistic analysis. Dark grey shading indicates those parameters that were used in the previous version of the model and were replaced with updated parameters in the current base case.

Table 33: Full list of parameters used within the model

Parameter name	Value (95% CI)	Distribution and parameters	Source
Progression from Stage 3–5 to RRT			
Rate of progression per patient-year of follow-up			
Age 15–24 years	0.143 (0.064, 0.319)	Lognormal: μ=-1.943; σ=0.408	Marks et al., 2012
Age 25–34 years	0.077 (0.043, 0.139)	Lognormal: μ=-2.561; σ=0.302	Marks et al., 2012
Age 35–44 years	0.063 (0.038, 0.104)	Lognormal: μ=-2.768; σ=0.258	Marks et al. 2012
Age 45–54 years	0.044 (0.030, 0.065)	Lognormal: μ=-3.119; σ=0.200	Marks et al., 2012
Age 55–64 years	0.022 (0.015, 0.031)	Lognormal: μ=-3.835; σ=0.183	Marks et al., 2012
Age 65–74 years	0.015 (0.011, 0.019)	Lognormal: μ=-4.227; σ=0.143	Marks et al., 2012
Age 75–84 years	0.007 (0.005, 0.009)	Lognormal: μ=-5.036; σ=0.171	Marks et al., 2012
Age 85–94 years	0.0049		Calculated
Age 95–104 years	0.0030		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Regression on ln(rate) for extrapolation:			
Intercept	-0.91		Calculated
Slope	-0.049		Calculated
3-month prob of progressing (Stage 3–5, pre-RRT, to Stage 5 RRT)			
Age 15–24 years	3.52%		Calculated
Age 25–34 years	1.91%		Calculated
Age 35–44 years	1.56%		Calculated
Age 45–54 years	1.10%		Calculated
Age 55–64 years	0.54%		Calculated
Age 65–74 years	0.36%		Calculated
Age 75–84 years	0.16%		Calculated
Age 85–94 years	0.12%		Calculated
Age 95–104 years	0.08%		Calculated
10-yr cumul incidence of progressing (Stage 3–4 to Stage 5)			
Age <69 years	7.0% (4.3%, 10.3%)	Beta: α=19; β=257	Eriksen & Ingebretsen, 2006
Age 70–79 years	4.0% (1.9%, 6.8%)	Beta: α=9; β=226	Eriksen & Ingebretsen, 2006
Age >79 years	3.0% (1.3%, 5.3%)	Beta: α=8; β=270	Eriksen & Ingebretsen, 2006
Total	4.0% (2.6%, 5.6%)	Beta: α=26; β=628	Eriksen & Ingebretsen, 2006
3-month prob of progressing (Stage 3–4 to Stage 5)			
Age <69 years	0.18%		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Age 70–79 years	0.10%		Calculated
Age >79 years	0.08%		Calculated
Total	0.10%		Calculated
Incidence of CI-AKI, baseline			
Prob CI-AKI (NaCl 0.9% + NAC)	11.5% (7.9%, 15.7%)	Beta: α=29; β=223	Maioli et al., 2008
Prob CI-AKI (NaCl 0.9%)	14.3% (3.2%, 31.7%)	Beta: α=3; β=18	Rashid et al., 2004
Pooled NaCl(0.9%) data from included RCTs			
Ln(odds)			
All	-1.89 (-1.97, -1.81)	Normal: μ=-1.89; σ=0.04	Sodium chloride 0.9% arms of trials
Elective	-2.11 (-2.21, -2.02)	Normal: μ=-2.11; σ=0.05	Sodium chloride 0.9% arms of trials
Emergency	-1.41 (-2.13, -0.69)	Normal: μ=-1.41; σ=0.37	Sodium chloride 0.9% arms of trials
Prob			
All	13.1%		Calculated
Elective	10.8%		Calculated
Emergency	19.6%		Calculated
Extreme values			
Minimum	2.2% (0.5%, 5.2%)	Beta: α=3; β=135	Mueller et al., 2002
Maximum	36.7% (20.7%, 54.3%)	Beta: α=11; β=19	Sadineni et al., 2017

Parameter name	Value (95% CI)	Distribution and parameters	Source
Prob CI-AKI, low estimate (2013 base case, 0.9% NaCl)	2.2% (0.5%, 5.2%)	Beta: α=3; β=135	Mueller et al., 2002
Prob CI-AKI, medium estimate (0.45% NaCl	19.2% (17.5%, 21.0%)	Beta: α=381; β=1599	Dangas et al., 2004
Prob CI-AKI, high estimate (0.45% NaCl)	30.0% (27.7%, 32.4%)	Beta: α=443; β=1033	Mehran et al., 2004
Post-CI-AKI mortality			
Maioli et al., 2012, 90-day mortality			
CI-AKI	7.2%	Not varied in PSA	Maioli et al., 2012
no CI-AKI	1.4%	Not varied in PSA	Maioli et al., 2012
ln(OR) CI-AKI -v- no CI-AKI	1.72 (0.99, 2.45)	Normal: μ=1.721; σ=0.373	Maioli et al., 2012
OR CI-AKI -v- no CI-AKI	5.59		Calculated
RD CI-AKI -v- no CI-AKI	5.8% (2.0%, 9.7%)	Normal: μ=0.058; σ=0.020	Maioli et al., 2012
Hoste et al., 2012, 90-day mortality			
CI-AKI	47.7%	Not varied in PSA	Hoste et al., 2011
no CI-AKI	18.7%	Not varied in PSA	Hoste et al., 2011
ln(OR) CI-AKI -v- no CI-AKI	1.38 (0.98, 1.78)	Normal: μ=1.378; σ=0.203	Hoste et al., 2011
OR CI-AKI -v- no CI-AKI	3.97		Calculated
RD CI-AKI -v- no CI-AKI	29.0% (19.8%, 38.1%)	Normal: μ=0.290; σ=0.047	Hoste et al., 2011
James et al., 2011, 90-day mortality			
Incidence of mortality @3mo (from graph), includes CKD and non-CKD pts			

Parameter name	Value (95% CI)	Distribution and parameters	Source
no CI-AKI	3.0% (2.7%, 3.3%)	Beta: α=402; β=12996	James et al., 2011
CI-AKI stage 1	9.5% (7.8%, 11.3%)	Beta: α=104; β=995	James et al., 2011
CI-AKI stage 2-3	21.5% (17.2%, 26.2%)	Beta: α=69; β=252	James et al., 2011
Proportions with CKD in whole cohort			
no CI-AKI	21.9% (21.2%, 22.6%)	Beta: α=2931; β=10467	James et al., 2011 (suppl)
CI-AKI stage 1	42.8% (39.9%, 45.7%)	Beta: α=470; β=629	James et al., 2011 (suppl)
CI-AKI stage 2-3	55.5% (50.0%, 60.8%)	Beta: α=178; β=143	James et al., 2011 (suppl)
Rates of mortality (per 100 person years), people with CKD			
no CI-AKI	7.4 (6.6, 8.2)	Lognormal: μ=2.0; σ=0.1	James et al., 2011
CI-AKI stage 1	19.2 (16.2, 22.8)	Lognormal: μ=3.0; σ=0.1	James et al., 2011
CI-AKI stage 2-3	34.3 (27.3, 43.1)	Lognormal: μ=3.5; σ=0.1	James et al., 2011
Rates of mortality (per 100 person years), people without CKD			
no CI-AKI	2.5 (2.3, 2.8)	Lognormal: μ=0.9; σ=0.1	James et al., 2011
CI-AKI stage 1	8.5 (6.9, 10.5)	Lognormal: μ=2.1; σ=0.1	James et al., 2011

Parameter name	Value (95% CI)	Distribution and parameters	Source
CI-AKI stage 2-3	27.9 (21.0, 37.1)	Lognormal: μ=3.3; σ=0.1	James et al., 2011
RR of mortality, CKD - v- no CKD			
no CI-AKI	2.96		Calculated
CI-AKI stage 1	2.26		Calculated
CI-AKI stage 2-3	1.23		Calculated
Risk of mortality, people without CKD			
no CI-AKI	2.1%		Calculated
CI-AKI stage 1	6.2%		Calculated
CI-AKI stage 2-3	19.1%		Calculated
Risk of mortality, people with CKD			
no CI-AKI	6.2%		Calculated
CI-AKI stage 1	13.9%		Calculated
CI-AKI stage 2-3	23.4%		Calculated
Prob mortality following CI-AKI in people with CKD	16.6%		Calculated
ln(OR) CI-AKI -v- no CI-AKI	1.097 (0.841, 1.353)	Normal: μ=1.10; σ=0.13	
OR CI-AKI -v- no CI-AKI	2.995		Calculated
RD CI-AKI -v- no CI-AKI	0.103 (0.074, 0.133)	Normal: μ=0.10; σ=0.02	
Probability of Stage 5 CKD post CI-AKI			
Incidence of ESRD @3mo (from graph), includes CKD and non-CKD pts			
no CI-AKI	0.0%	Not varied in PSA	James et al., 2011

Parameter name	Value (95% CI)	Distribution and parameters	Source
CI-AKI stage 1	1.0% (0.5%, 1.7%)	Beta: α=11; β=1088	James et al., 2011
CI-AKI stage 2-3	5.4% (3.2%, 8.1%)	Beta: α=17; β=304	James et al., 2011
Proportions with CKD in whole cohort			
no CI-AKI	21.9% (21.2%, 22.6%)	Beta: α=2931; β=10467	James et al., 2011 (suppl)
CI-AKI stage 1	42.8% (39.9%, 45.7%)	Beta: α=470; β=629	James et al., 2011 (suppl)
CI-AKI stage 2-3	55.5% (50.0%, 60.8%)	Beta: α=178; β=143	James et al., 2011 (suppl)
Rates of ESRD (per 100 person years), people with CKD			
no CI-AKI	0.50 (0.35, 0.71)	Lognormal: μ=-1; σ=0	James et al., 2011
CI-AKI stage 1	3.40 (2.40, 4.81)	Lognormal: μ=1; σ=0	James et al., 2011
CI-AKI stage 2-3	22.00 (15.99, 30.27)	Lognormal: μ=3; σ=0	James et al., 2011
Rates of ESRD (per 100 person years), people without CKD			
no CI-AKI	0.20 (0.08, 0.49)	Lognormal: μ=-2; σ=0	James et al., 2011
CI-AKI stage 1	0.40 (0.17, 0.94)	Lognormal: μ=-1; σ=0	James et al., 2011
CI-AKI stage 2-3	0.60 (0.09, 3.93)	Lognormal: μ=-1; σ=1	James et al., 2011
RR of ESRD, CKD - v- no CKD			

Parameter name	Value (95% CI)	Distribution and parameters	Source
no CI-AKI	2.50		Calculated
CI-AKI stage 1	8.50		Calculated
CI-AKI stage 2–3	36.67		Calculated
Risk of ESRD, people without CKD			
no CI-AKI	0.00%		Calculated
CI-AKI stage 1	0.24%		Calculated
CI-AKI stage 2–3	0.26%		Calculated
Risk of ESRD, people with CKD			
no CI-AKI	0.00%		Calculated
CI-AKI stage 1	2.02%		Calculated
CI-AKI stage 2–3	9.53%		Calculated
Prob ESRD following CI-AKI in people with CKD	4.08%		Calculated
Prob progression	3.28%	Not varied in PSA	James et al., 2012
Risk of CI-AKI from repeat scans			
Repeat scan prob over follow up period	8.34% (7.02%, 9.89%)	Lognormal: μ=-2.48; σ=0.09	Chan et al., 2015
Repeat scan rate per cycle, Chan	2.06%		Calculated
Repeat scan rate per cycle, James (old version of model)	2.99%	Not varied in PSA	James et al., 2012
Mortality: Stages 3–5 CKD			
Standardised mortality ratios Stages 3–5			
Men			
Age <69 years	3.60	Not varied in PSA	Eriksen & Ingebretsen, 2006

Parameter name	Value (95% CI)	Distribution and parameters	Source
Age 70–79 years	2.40	Not varied in PSA	Eriksen & Ingebretsen, 2006
Age >79 years	2.30	Not varied in PSA	Eriksen & Ingebretsen, 2006
Women			
Age <69 years	2.70	Not varied in PSA	Eriksen & Ingebretsen, 2006
Age 70–79 years	1.80	Not varied in PSA	Eriksen & Ingebretsen, 2006
Age >79 years	2.10	Not varied in PSA	Eriksen & Ingebretsen, 2006
Mortality: RRT			
Relative risk of death compared with gen pop			
Age 20–24 years	24.7	Not varied in PSA	UK Renal Registry, 2018
Age 25–29 years	23.0	Not varied in PSA	UK Renal Registry, 2018
Age 30–34 years	21.0	Not varied in PSA	UK Renal Registry, 2018
Age 35–39 years	21.2	Not varied in PSA	UK Renal Registry, 2018
Age 40–44 years	16.6	Not varied in PSA	UK Renal Registry, 2018
Age 45–49 years	15.8	Not varied in PSA	UK Renal Registry, 2018
Age 50–54 years	12.7	Not varied in PSA	UK Renal Registry, 2018
Age 55–59 years	11.4	Not varied in PSA	UK Renal Registry, 2018
Age 60–64 years	9.7	Not varied in PSA	UK Renal Registry, 2018
Age 65–69 years	8.9	Not varied in PSA	UK Renal Registry, 2018
Age 70–74 years	7.8	Not varied in PSA	UK Renal Registry, 2018
Age 75–79 years	5.9	Not varied in PSA	UK Renal Registry, 2018
Age 80–84 years	4.9	Not varied in PSA	UK Renal Registry, 2018
Age 85+ years	4.9	Not varied in PSA	
Old model: Standardised mortality ratios Stage 5			

Parameter name	Value (95% CI)	Distribution and parameters	Source
Men			
Age 18–64 years	8.9	Not varied in PSA	Villar et al., 2007
Age 65+ years	4.9	Not varied in PSA	Villar et al., 2007
Women			
Age 18–64 years	13.9	Not varied in PSA	Villar et al., 2007
Age 65+ years	8.0	Not varied in PSA	Villar et al., 2007
Treatment effects			
ln(OR) -v- no (intravenous) hydration			
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	-0.821	Multivariate normal	Clinical review
NAC (IV bolus) + sodium chloride 0.9% (IV)	-0.773	Multivariate normal	Clinical review
NAC (IV) + sodium chloride 0.45% (IV)	-0.582	Multivariate normal	Clinical review
NAC (IV) + sodium chloride 0.9% (IV)	-0.414	Multivariate normal	Clinical review
NAC (oral)	0.036	Multivariate normal	Clinical review
NAC (oral) + sodium bicarbonate (IV)	-0.472	Multivariate normal	Clinical review
NAC (oral) + sodium chloride 0.45% (IV)	-0.615	Multivariate normal	Clinical review
NAC (oral) + sodium chloride 0.9% (IV)	-0.560	Multivariate normal	Clinical review
Oral fluids	-0.868	Multivariate normal	Clinical review
Sodium bicarbonate (IV)	-0.610	Multivariate normal	Clinical review
Sodium bicarbonate (oral) + oral fluids	-2.089	Multivariate normal	Clinical review
Sodium chloride 0.45% (IV)	0.258	Multivariate normal	Clinical review
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	0.551	Multivariate normal	Clinical review
Sodium chloride 0.9% (IV)	-0.344	Multivariate normal	Clinical review
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	-0.889	Multivariate normal	Clinical review

Parameter name	Value (95% CI)	Distribution and parameters	Source
Sodium citrate (oral)	0.134	Multivariate normal	Clinical review
ln(OR) -v- baseline (NAC (oral) + sodium chloride 0.9% (IV))			
No (intravenous) hydration	0.560		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	-0.261		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	-0.213		Calculated
NAC (IV) + sodium chloride 0.45% (IV)	-0.022		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	0.146		Calculated
NAC (oral)	0.596		Calculated
NAC (oral) + sodium bicarbonate (IV)	0.088		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	-0.056		Calculated
NAC (oral) + sodium chloride 0.9% (IV)	0.000		Calculated
Oral fluids	-0.309		Calculated
Sodium bicarbonate (IV)	-0.050		Calculated
Sodium bicarbonate (oral) + oral fluids	-1.529		Calculated
Sodium chloride 0.45% (IV)	0.818		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	1.110		Calculated
Sodium chloride 0.9% (IV)	0.216		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	-0.329		Calculated
Sodium citrate (oral)	0.694		Calculated
ln(odds) of AKI			
No (intravenous) hydration	-1.480		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	-2.301		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	-2.253		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
NAC (IV) + sodium chloride 0.45% (IV)	-2.062		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	-1.894		Calculated
NAC (oral)	-1.444		Calculated
NAC (oral) + sodium bicarbonate (IV)	-1.952		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	-2.096		Calculated
NAC (oral) + sodium chloride 0.9% (IV)	-2.040		Calculated
Oral fluids	-2.349		Calculated
Sodium bicarbonate (IV)	-2.090		Calculated
Sodium bicarbonate (oral) + oral fluids	-3.569		Calculated
Sodium chloride 0.45% (IV)	-1.222		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	-0.930		Calculated
Sodium chloride 0.9% (IV)	-1.824		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	-2.369		Calculated
Sodium citrate (oral)	-1.346		Calculated
Probability of AKI			
No (intravenous) hydration	18.54%		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	9.10%		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	9.51%		Calculated
NAC (IV) + sodium chloride 0.45% (IV)	11.28%		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	13.08%		Calculated
NAC (oral)	19.10%		Calculated
NAC (oral) + sodium bicarbonate (IV)	12.43%		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	10.95%		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
NAC (oral) + sodium chloride 0.9% (IV)	11.51%		Calculated
Oral fluids	8.72%		Calculated
Sodium bicarbonate (IV)	11.01%		Calculated
Sodium bicarbonate (oral) + oral fluids	2.74%		Calculated
Sodium chloride 0.45% (IV)	22.76%		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	28.30%		Calculated
Sodium chloride 0.9% (IV)	13.89%		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	8.56%		Calculated
Sodium citrate (oral)	20.65%		Calculated
Costs: health states summary			
AKI state	£3617.17		Calculated
CKD 3–5 state	£270.51		Calculated
CKD 5 state cycle 1	£40587.77		Calculated
CKD 5 state cycle 2 onwards	£4788.44		Calculated
Unit costs			
AKI			
LA07H Acute Kidney Injury with Interventions, with CC Score 11+	£6312.78	Not varied in PSA	NHS Improvement, 2018
LA07J Acute Kidney Injury with Interventions, with CC Score 6–10	£4731.26	Not varied in PSA	NHS Improvement, 2018
LA07K Acute Kidney Injury with Interventions, with CC Score 0–5	£3697.84	Not varied in PSA	NHS Improvement, 2018
LA07L Acute Kidney Injury without Interventions, with CC Score 12+	£2797.95	Not varied in PSA	NHS Improvement, 2018

Parameter name	Value (95% CI)	Distribution and parameters	Source
LA07M Acute Kidney Injury without Interventions, with CC Score 8–11	£2053.66	Not varied in PSA	NHS Improvement, 2018
LA07N Acute Kidney Injury without Interventions, with CC Score 4–7	£1502.27	Not varied in PSA	NHS Improvement, 2018
LA07P Acute Kidney Injury without Interventions, with CC Score 0–3	£1060.83	Not varied in PSA	NHS Improvement, 2018
Pooled average	£1865.01		Calculated
AKI requiring RRT			
LE01A Haemodialysis for Acute Kidney Injury, 19 years and over	£271.00	Not varied in PSA	NHS Improvement, 2018
LE02A Peritoneal Dialysis for Acute Kidney Injury, 19 years and over	£97.00	Not varied in PSA	NHS Improvement, 2018
Pooled average	£267.91		Calculated
Haemodialysis			
LD01A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£151.44	Not varied in PSA	NHS Improvement, 2018
LD01A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over, away from base	£147.39	Not varied in PSA	NHS Improvement, 2018
LD03A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	£159.05	Not varied in PSA	NHS Improvement, 2018
LD05A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£138.12	Not varied in PSA	NHS Improvement, 2018
LD05A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over, awawy from base	£227.65	Not varied in PSA	NHS Improvement, 2018

Parameter name	Value (95% CI)	Distribution and parameters	Source
LD07A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	£130.64	Not varied in PSA	NHS Improvement, 2018
LD09A Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£302.85	Not varied in PSA	NHS Improvement, 2018
LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£161.05	Not varied in PSA	NHS Improvement, 2018
LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£171.65	Not varied in PSA	NHS Improvement, 2018
LD04A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	£180.91	Not varied in PSA	NHS Improvement, 2018
LD06A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£148.21	Not varied in PSA	NHS Improvement, 2018
LD06A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£245.15	Not varied in PSA	NHS Improvement, 2018
LD08A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	£151.97	Not varied in PSA	NHS Improvement, 2018
LD10A Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£201.33	Not varied in PSA	NHS Improvement, 2018
LD10A Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£115.17	Not varied in PSA	NHS Improvement, 2018
Pooled average per session (haemodialysis)	£153.36		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Haemodialysis - initial access procedure			
YR41A Insertion of Tunnelled Central Venous Catheter, 19 years and over	£848.38	Not varied in PSA	NHS Improvement, 2018
YQ42Z Open Arteriovenous Fistula, Graft or Shunt Procedures	£2345.06	Not varied in PSA	NHS Improvement, 2018
Average weighted by haemodialysis access type	£1842.45		Calculated
Peritoneal dialysis			
LD11A Continuous Ambulatory Peritoneal Dialysis, 19 years and over	£67.60	Not varied in PSA	NHS Improvement, 2018
LD11A Continuous Ambulatory Peritoneal Dialysis, 19 years and over, away from base	£62.45	Not varied in PSA	NHS Improvement, 2018
LD12A Automated Peritoneal Dialysis, 19 years and over	£76.61	Not varied in PSA	NHS Improvement, 2018
LD12A Automated Peritoneal Dialysis, 19 years and over, away from base	£69.74	Not varied in PSA	NHS Improvement, 2018
LD13A Assisted Automated Peritoneal Dialysis, 19 years and over	£84.44	Not varied in PSA	NHS Improvement, 2018
LD13A Assisted Automated Peritoneal Dialysis, 19 years and over, away from base	£78.08	Not varied in PSA	NHS Improvement, 2018
Pooled average (peritoneal dialysis)	£74.35		Calculated
Peritoneal dialysis - associated procedures			
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1694.60	Not varied in PSA	NHS Improvement, 2018
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1818.23	Not varied in PSA	NHS Improvement, 2018
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1029.78	Not varied in PSA	NHS Improvement, 2018

Parameter name	Value (95% CI)	Distribution and parameters	Source
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£908.02	Not varied in PSA	NHS Improvement, 2018
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£167.84	Not varied in PSA	NHS Improvement, 2018
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£158.92	Not varied in PSA	NHS Improvement, 2018
Pooled average peritoneal dialysis associated procedures	£860.00		Calculated
Transplantation work-up			
LA11Z Kidney Pre-Transplantation Workup of Live Donor	£254.68	Not varied in PSA	NHS Improvement, 2018
LA12A Kidney Pre-Transplantation Workup of Recipient, 19 years and over	£277.77	Not varied in PSA	NHS Improvement, 2018
Average work-up per transplant	£1868.98		Calculated
Transplantation procedure			
LB46Z Live Donation of Kidney	£7027.00	Not varied in PSA	NHS Improvement, 2018
LA01A Kidney Transplant, 19 years and over, from Cadaver Non-Heart-Beating Donor	£13165.83	Not varied in PSA	NHS Improvement, 2018
LA02A Kidney Transplant, 19 years and over, from Cadaver Heart-Beating Donor	£12555.28	Not varied in PSA	NHS Improvement, 2018
LA03A Kidney Transplant, 19 years and over, from Live Donor	£13058.95	Not varied in PSA	NHS Improvement, 2018
Pooled average kidney transplant procedure	£14793.66		Calculated
Total average kidney transplant	£16662.64		Calculated
Excess bed days for cardiac catheterisation: elective inpatient			
EY42A Complex Cardiac Catheterisation with CC Score 7+	£623.95	Not varied in PSA	NHS Improvement, 2018
EY42B Complex Cardiac Catheterisation with CC Score 4–6	£600.13	Not varied in PSA	NHS Improvement, 2018
EY42C Complex Cardiac Catheterisation with CC Score 2–3	£239.48	Not varied in PSA	NHS Improvement, 2018

Parameter name	Value (95% CI)	Distribution and parameters	Source
EY42D Complex Cardiac Catheterisation with CC Score 0–1	£212.52	Not varied in PSA	NHS Improvement, 2018
EY43A Standard Cardiac Catheterisation with CC Score 13+	£451.16	Not varied in PSA	NHS Improvement, 2018
EY43B Standard Cardiac Catheterisation with CC Score 10–12	£427.65	Not varied in PSA	NHS Improvement, 2018
EY43C Standard Cardiac Catheterisation with CC Score 7–9	£486.55	Not varied in PSA	NHS Improvement, 2018
EY43D Standard Cardiac Catheterisation with CC Score 4–6	£345.99	Not varied in PSA	NHS Improvement, 2018
EY43E Standard Cardiac Catheterisation with CC Score 2–3	£409.54	Not varied in PSA	NHS Improvement, 2018
EY43F Standard Cardiac Catheterisation with CC Score 0–1	£569.81	Not varied in PSA	NHS Improvement, 2018
Excess bed days for cardiac catheterisation: non-elective			
EY42A Complex Cardiac Catheterisation with CC Score 7+	£465.99	Not varied in PSA	NHS Improvement, 2018
EY42B Complex Cardiac Catheterisation with CC Score 4–6	£385.28	Not varied in PSA	NHS Improvement, 2018
EY42C Complex Cardiac Catheterisation with CC Score 2–3	£428.14	Not varied in PSA	NHS Improvement, 2018
EY42D Complex Cardiac Catheterisation with CC Score 0–1	£399.83	Not varied in PSA	NHS Improvement, 2018
EY43A Standard Cardiac Catheterisation with CC Score 13+	£341.98	Not varied in PSA	NHS Improvement, 2018
EY43B Standard Cardiac Catheterisation with CC Score 10–12	£356.92	Not varied in PSA	NHS Improvement, 2018
EY43C Standard Cardiac Catheterisation with CC Score 7–9	£341.88	Not varied in PSA	NHS Improvement, 2018
EY43D Standard Cardiac Catheterisation with CC Score 4–6	£385.06	Not varied in PSA	NHS Improvement, 2018
EY43E Standard Cardiac Catheterisation with CC Score 2–3	£354.30	Not varied in PSA	NHS Improvement, 2018
EY43F Standard Cardiac Catheterisation with CC Score 0–1	£366.02	Not varied in PSA	NHS Improvement, 2018
Pooled average	£378.77		Calculated
Appointments and tests			
First appt nephrology – consultant led	£181.11	Not varied in PSA	NHS Improvement, 2018
Follow up appt nephrology - consultant led	£233.28	Not varied in PSA	NHS Improvement, 2018
Follow up appt nephrology - non-consultant led	£118.36	Not varied in PSA	NHS Improvement, 2018

Parameter name	Value (95% CI)	Distribution and parameters	Source
Specialist clinical nurse - cost per hour (Band 6)	£74.00	Not varied in PSA	Curtis & Burns, 2018
Home consultation (25 min)	£30.83		Calculated
Phone consultation (6 min)	£6.17		Calculated
Biochemistry	£1.11	Not varied in PSA	NHS Improvement, 2018
Phlebotomy	£2.83	Not varied in PSA	NHS Improvement, 2018
eGFR measurement	£3.94		Calculated
Drugs associated with health states			
Diuretics (furosemide)			
40 mg tablets furosemide, pack of 28	£0.70 (£0.70, £0.70)	Gamma: α=1026691; β=0	Commercial Medicines Unit, 2019
Per 40 mg tablet	£0.03		Calculated
Epoetin alfa			
Average dose - units per week	1788 (1715, 1861)	Normal: μ=1788; σ=37	NICE, 2015
Average cost per unit	£0.01		Calculated
Eprex 1,000units/0.5ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 2,000units/0.5ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 10,000units/1ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 3,000units/0.3ml	£0.02	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 4,000units/0.4ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 5,000units/0.5ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 6,000units/0.6ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 8,000units/0.8ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 20,000units/0.5ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a

Parameter name	Value (95% CI)	Distribution and parameters	Source
Eprex 30,000units/0.75ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Eprex 40,000units/1ml	£0.01	Not varied in PSA	NHS Business Services Authority, 2019a
Epoetin alfa (cost per cycle)	£240.17		Calculated
Post-transplantation immunosuppression			
Basiliximab induction			
20mg vial (adult dose)	£842.38	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Number of doses	1.96 (1.93, 2.00)	Normal: μ=1.96; σ=0.02	Brennan et al., (2006)
First infusion (SB12Z)	£228.99	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Subsequent infusion (SB15Z)	£289.33	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Cost per person	£2162.33		Calculated
Maintenance			
Prograf 500microgram capsules	£61.88	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Prograf 1mg capsules	£80.28	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for

Parameter name	Value (95% CI)	Distribution and parameters	Source
			weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Prograf 5mg capsules	£296.58	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Adoport 500microgram capsules	£42.92	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Adoport 1mg capsules	£55.69	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Adoport 5mg capsules	£205.74	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Weighted average cost per mg	£1.54		Calculated
Dose (mg/kg/day)	0.20	Not varied in PSA	Jones-Hughes et al., 2016
Weight (kg)	70	Not varied in PSA	Assumption
Tacrolimus Cost per cycle	£1973.55		Calculated
Ciclosporin 10mg capsules	£18.25	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Ciclosporin 25mg capsules	£18.37	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Ciclosporin 50mg capsules	£35.97	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Ciclosporin 100mg capsules	£68.28	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Sandimmun_Cap 25mg	£29.58	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Sandimmun_Cap 100mg	£109.93	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Sandimmun_Cap 50mg	£57.92	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Deximune_Cap 25mg	£13.06	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Deximune_Cap 50mg	£25.60	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Deximune_Cap 100mg	£48.90	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Capimune_Cap 25mg	£13.05	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Capimune_Cap 50mg	£25.50	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Capimune_Cap 100mg	£48.50	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Capsorin_Cap 100mg	£41.59	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Capsorin_Cap 50mg	£21.80	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Capsorin_Cap 25mg	£11.14	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Vanquoral_Cap 10mg	£12.75	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Vanquoral_Cap 25mg	£13.05	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Vanquoral_Cap 50mg	£25.59	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Vanquoral_Cap 100mg	£48.89	Not varied in PSA	Cost from British National Formulary (Joint Formulary Committee, 2019); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Weighted average cost per mg	£0.02		Calculated
Dose (mg/kg/day)	4.0	Not varied in PSA	Jones-Hughes et al., 2016
Weight (kg)	70	Not varied in PSA	Assumption
Ciclosporin cost per cycle	£605.11		Calculated
Azathioprine 25mg tablets	£1.53	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for

Parameter name	Value (95% CI)	Distribution and parameters	Source
			weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Azathioprine 50mg tablets	£2.17	Not varied in PSA	Cost from NHS Drug Tariff (NHS Business Services Authority, 2019a); quantity for weighting from Prescription Cost Analysis (NHS Business Services Authority, 2019b)
Weighted average cost per mg	£0.00		Calculated
Dose (mg/kg/day)	1.75	Not varied in PSA	Jones-Hughes et al., 2016
Weight (kg)	70	Not varied in PSA	Assumption
Azathioprine cost per cycle	£11.18		Calculated
Total costs per cycle			
Proportion of people on tacrolimus -v- ciclosporin	75.0%	Not varied in PSA	NICE, 2013b
Induction costs at time of Tx	£2162.33		Calculated
Maintenance	£1642.62		Calculated
Proportions of patients in each CKD Stage			
Stage 3	70.0%	Not varied in PSA	NICE, 2013a
Stage 4	25.0%	Not varied in PSA	NICE, 2013a
Stage 5	5.0%	Not varied in PSA	NICE, 2013a
On RRT	61.0%	Not varied in PSA	Hussain et al., 2013
On RRT - SA	81.6%	Not varied in PSA	Chandna et al., 2010
Cost of AKI			
Temporary RRT following CI-AKI			
Odds of people with AKI requiring temporary dialysis	0.333	Not varied in PSA	Kama et al., 2014
Odds of people with AKI requiring temporary dialysis	0.067	Not varied in PSA	Briguori et al., 2002

Parameter name	Value (95% CI)	Distribution and parameters	Source
Odds of people with AKI requiring temporary dialysis	0.182	Not varied in PSA	Briguori et al., 2007
Pooled odds	0.212 (0.093, 0.485)	Lognormal: μ=-1.55; σ=0.42	
Probability	17.53%		Calculated
No. haemodialysis sessions required	2 (1, 3)	Triangular: min=1; mode=2; max=3	Committee assumption
Cost of haemodialysis for temporary AKI	£542.00		Calculated
Cost of temporary dialysis for AKI	£94.99		Calculated
Permanent RRT following CI-AKI	£1657.17		Calculated
Total cost of AKI	£3617.17		Calculated
Cost of CKD 3–5			
Proportion in Stage 3	72.2%		Calculated
Proportion in Stage 4	25.8%		Calculated
Proportion in Stage 5 pre-dialysis	2.0%		Calculated
Stages 3–4			
No. nephrology appointments per cycle	1	Not varied in PSA	NICE, 2013a
Cost of nephrology appointments	£233.28		Calculated
No. eGFR measurements per cycle	1	Not varied in PSA	NICE, 2013a
Total eGFR measurement costs per cycle	£3.94		Calculated
Percentage in Stage 3–4 receiving epoetin (with anaemia)	9.0%	Not varied in PSA	NICE, 2013a
Total cost epoeitin	£21.61		Calculated
Percentage in Stage 4 receiving furosemide	60.0%	Not varied in PSA	NICE, 2013a
Total furosemide cost per cycle	£1.37		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Total cost Stages 3–4	£260.20		Calculated
Stage 5 - pre-dialysis			
No follow up appointments (cons led) per cycle	2	Not varied in PSA	NICE, 2013a
Total cost of appointments	£466.55		Calculated
eGFR test frequency	13.04	Not varied in PSA	
Total cost of eGFR tests	£51.41		Calculated
Epoetin			
Percentage in Stage 5 receiving epoetin (with anaemia)	33.3%	Not varied in PSA	NICE, 2013a
Total cost of epoetin	£80.05		Calculated
Diuretics			
Percentage in Stage 5 receiving furosemide	90.0%	Not varied in PSA	NICE, 2013a
Number of furosemide pills Stage 5 (80 mg)	2	Not varied in PSA	
Total furosemide cost per cycle	£1.70		Calculated
Phone calls	13.04	Not varied in PSA	NICE, 2013a
Total cost of phone calls	£80.44		Calculated
Home visits	3	Not varied in PSA	NICE, 2013a
Total cost of home visits	£92.50		Calculated
Total cost Stage 5 pre-dialysis	£772.65		Calculated
Proportion in Stages 3–4	98.0%		Calculated
Proportion in Stage 5 pre-dialysis	2.0%		Calculated
Total cost of CKD 3–5	£270.51		Calculated
Probability of being added to the transplant waiting list by age			

Parameter name	Value (95% CI)	Distribution and parameters	Source
Prob of being waitlisted	56.97% (55.91%, 58.02%)	Beta: α=4814; β=3636	NHS Blood and Transplant, 2018
Odds of being waitlisted	1.324		Calculated
ORs			
18–29	1.00	Not varied in PSA	UK Renal Registry, 2018
30–39	0.73 (0.59, 0.91)	Lognormal: μ=-0.315; σ=0.111	UK Renal Registry, 2018
40–49	0.48 (0.40, 0.58)	Lognormal: μ=-0.734; σ=0.099	UK Renal Registry, 2018
50–59	0.28 (0.23, 0.34)	Lognormal: μ=-1.273; σ=0.100	UK Renal Registry, 2018
60–64	0.14 (0.11, 0.17)	Lognormal: μ=-1.966; σ=0.111	UK Renal Registry, 2018
65–74	0.073		Calculated
75–84	0.024		Calculated
85–94	0.007		Calculated
95–104	0.002		Calculated
Odds			
18–29	3.19		Calculated
30–39	2.33		Calculated
40–49	1.53		Calculated
50–59	0.89		Calculated
60–64	0.45		Calculated
65–74	0.23		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
75–84	0.078		Calculated
85–94	0.022		Calculated
95–104	0.0051		Calculated
Prob of being waitlisted			
18–29	76.1%		Calculated
30–39	69.9%		Calculated
40–49	60.5%		Calculated
50–59	47.2%		Calculated
60–64	30.9%		Calculated
65–74	18.8%		Calculated
75–84	7.2%		Calculated
85–94	2.1%		Calculated
95–104	0.50%		Calculated
Cost of RRT			
Cycle 1 resource use and costs			
First appointment - consultant led, no. per cycle	1	Not varied in PSA	NICE, 2013a
Follow up appointments - consultant led, no. per cycle	1	Not varied in PSA	NICE, 2013a
Total cost of appointments	£414.39		Calculated
eGFR tests, no. per cycle	13.04	Not varied in PSA	NICE, 2013a
Total cost of eGFR tests	£51.41		Calculated
Epoetin			
Percentage in Stage 5 receiving epoetin (with anaemia)	33.33%	Not varied in PSA	NICE, 2013a
Total cost of epoetin	£80.05		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Dialysis			
Frequency of haemodialysis per week	3	Not varied in PSA	NICE, 2013a
Frequency of peritoneal dialysis per week	7	Not varied in PSA	NICE, 2013a
Proportion of total dialysis costs for travel, access maintenance, etc.	15.00%	Triangular: min=0%; mode=15 %; max=30%	NICE, 2018 (assumption)
Per cycle average cost of dialysis	£7181.33		Calculated
Cost of initial access procedures	£1714.31		Calculated
Total cost of dialysis, first cycle	£8895.63		Calculated
Weighted dialysis vs Tx	£4091.99		Calculated
Transplantation			
Waiting time to kidney transplant (days)	782.00 (764.00, 800.00)	Normal: μ=782; σ=9	NHS Blood and Transplant, 2018
Waiting time to kidney transplant (years)	2.14		Calculated
Discounted	2.06		Calculated
Discounted cost of kidney transplant	£15479.48		Calculated
Cost of dialysis initiation (assumes pre-Tx dialysis required)	£1714.31		Calculated
Cost of ongoing dialysis until Tx received	£59290.57		Calculated
Cost of immunosuppressants, first cycle	£3651.41		Calculated
Cost of immunosuppressants until Tx received (to be subtracted)	£13561.83		Calculated
Total cost of Tx, first cycle	£66573.95		Calculated
Weighted dialysis vs Tx	£35949.93		Calculated
Additional cost for cycle 1	£545.85		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Total cost for cycle 1	£40587.77		Calculated
Cycle 2 onwards resource use and costs			
Follow up appointments - consultant led	2	Not varied in PSA	
Total cost of appointments	£466.55		Calculated
eGFR tests	13.04	Not varied in PSA	
Total cost of eGFR tests	£51.41		Calculated
Epoetin			
Percentage in Stage 5 receiving epoetin (with anaemia)	33.33%	Not varied in PSA	
Total cost of epoetin	£80.05		Calculated
Total dialysis	£7181.33		Calculated
Weighted dialysis vs Tx	£3303.41		Calculated
Total transplantation (ongoing immunosuppressant costs)	£1642.62		Calculated
Weighted dialysis vs Tx	£887.01		Calculated
Additional cost for cycle 1	£598.01		Calculated
Total cost for cycle 2 onwards	£4788.44		Calculated
Intervention costs: fluid unit costs			
Sodium chloride			
Sodium chloride 0.9%, 500 ml, BNF	£2.70	Not varied in PSA	Joint Formulary Committee, 2019 (Polyfusor SB)
Sodium chloride 0.9%, 500 ml, CMU	£0.75	Not varied in PSA	Commercial Medicines Unit, personal communication via email, June 2019
Sodium chloride 0.9%, 1000 ml, BNF	£3.59	Not varied in PSA	Joint Formulary Committee, 2019 (Polyfusor SB)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Sodium chloride 0.9%, 1000 ml, CMU	£0.92	Not varied in PSA	Commercial Medicines Unit, personal communication via email, June 2019
Sodium chloride 0.45%, 500 ml, BNF	£3.98	Not varied in PSA	Joint Formulary Committee, 2019 (Polyfusor SB)
Sodium chloride 0.45%, 500 ml, CMU	£1.00	Not varied in PSA	Commercial Medicines Unit, personal communication via email, June 2019
Sodium bicarbonate			
IV 1.26%, 500 ml	£11.41	Not varied in PSA	Joint Formulary Committee, 2019 (Polyfusor sodium bicarbonate)
500 mg capsules	£0.02	Not varied in PSA	Commercial Medicines Unit, 2019
Oral fluids	£0.00	Not varied in PSA	
Sodium citrate (30 ml 0.3M oral solution)	£2.38	Not varied in PSA	Commercial Medicines Unit, 2019
Acetylcysteine			
Capsules 600mg	£1.33	Not varied in PSA	NHS Business Services Authority, 2019a
Solution for infusion 10 ml of 2g/10ml, Tariff	£2.13	Not varied in PSA	NHS Business Services Authority, 2019a
Solution for infusion 10 ml of 2g/10ml, CMU	£0.80	Not varied in PSA	Commercial Medicines Unit, personal communication via email, June 2019
Intervention costs: fluid strategy costs			
Base case (with bed days for all IV)			
No (intravenous) hydration	£0.00		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£389.81		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	£384.49		Calculated
NAC (IV) + sodium chloride 0.45% (IV)	£396.82		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	£384.49		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
NAC (oral)	£5.32		Calculated
NAC (oral) + sodium bicarbonate (IV)	£406.91		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	£400.01		Calculated
NAC (oral) + sodium chloride 0.9% (IV)	£387.68		Calculated
Oral fluids	£0.00		Calculated
Sodium bicarbonate (IV)	£401.59		Calculated
Sodium bicarbonate (oral) + oral fluids	£0.26		Calculated
Sodium chloride 0.45% (IV)	£394.69		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£417.51		Calculated
Sodium chloride 0.9% (IV)	£382.36		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£407.88		Calculated
Sodium citrate (oral)	£2.38		Calculated
Fluid strategy costs, sensitivity analysis (bed days for selected interventions only)			
No (intravenous) hydration	£0.00		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£11.04		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	£5.72		Calculated
NAC (IV) + sodium chloride 0.45% (IV)	£396.82		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	£5.72		Calculated
NAC (oral)	£5.32		Calculated
NAC (oral) + sodium bicarbonate (IV)	£28.14		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	£400.01		Calculated
NAC (oral) + sodium chloride 0.9% (IV)	£8.91		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Oral fluids	£0.00		Calculated
Sodium bicarbonate (IV)	£22.82		Calculated
Sodium bicarbonate (oral) + oral fluids	£0.26		Calculated
Sodium chloride 0.45% (IV)	£394.69		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£417.51		Calculated
Sodium chloride 0.9% (IV)	£3.59		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£407.88		Calculated
Sodium citrate (oral)	£2.38		Calculated
Fluid strategy costs, sensitivity analysis (all inpatient)			
No (intravenous) hydration	£0.00		Calculated
NAC (IV bolus & oral) + sodium chloride 0.9% (IV)	£11.04		Calculated
NAC (IV bolus) + sodium chloride 0.9% (IV)	£5.72		Calculated
NAC (IV) + sodium chloride 0.45% (IV)	£18.05		Calculated
NAC (IV) + sodium chloride 0.9% (IV)	£5.72		Calculated
NAC (oral)	£5.32		Calculated
NAC (oral) + sodium bicarbonate (IV)	£28.14		Calculated
NAC (oral) + sodium chloride 0.45% (IV)	£21.24		Calculated
NAC (oral) + sodium chloride 0.9% (IV)	£8.91		Calculated
Oral fluids	£0.00		Calculated
Sodium bicarbonate (IV)	£22.82		Calculated
Sodium bicarbonate (oral) + oral fluids	£0.26		Calculated
Sodium chloride 0.45% (IV)	£15.92		Calculated
Sodium chloride 0.45% (IV) + sodium bicarbonate (IV)	£38.74		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Sodium chloride 0.9% (IV)	£3.59		Calculated
Sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	£29.11		Calculated
Sodium citrate (oral)	£2.38		Calculated
Utilities			
Proportion on dialysis versus transplant	46.00%	Not varied in PSA	UK Renal Registry, 2018
Proportion on haemodialysis versus peritoneal	86.96%	Not varied in PSA	UK Renal Registry, 2018
CKD utility values			
Stage 3	0.80 (0.62, 0.93)	Beta: α=19; β=5	Jesky et al., 2016
Stage 4	0.74 (0.62, 0.85)	Beta: α=41; β=14	Jesky et al., 2016
Stage 5, conservative management	0.73 (0.52, 0.90)	Beta: α=15; β=5	Jesky et al., 2016
Stage 5, RRT (haemodialysis)	0.56 (0.49, 0.62)	Beta: α=125; β=98	Liem et al., 2008
Stage 5, RRT (peritoneal dialysis)	0.58 (0.49, 0.66)	Beta: α=75; β=54	Liem et al., 2008
Stage 5, RRT (transplanted)	0.81 (0.71, 0.89)	Beta: α=58; β=14	Liem et al., 2008
AKI utility values			
EQ-5D index at 6 months, AKI	0.68 (0.42, 0.89)	Beta: α=9; β=4	Nisula et al., 2013
EQ-5D index at 6 months, gen pop at study cohort age	0.83 (0.80, 0.85)	Beta: α=825; β=174	Nisula et al., 2013
Proportional decrement for AKI	0.82	Not varied in PSA	

Parameter name	Value (95% CI)	Distribution and parameters	Source
QALYs per cycle			
Stage 3–5	0.20		Calculated
RRT	0.17		Calculated

References

Brennan DC, Daller JA, Lake KD et al. (2006) Rabbit antithymocyte globulin versus basiliximab in renal transplantation. The New England journal of medicine 355(19): 1967-1977.

Briguori C, Airoldi F, D'Andrea D et al. (2007) Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation 115(10): 1211-1217.

Briguori C, Manganelli F, Scarpato P et al. (2002) Acetylcysteine and contrast agent-associated nephrotoxicity. Journal of the American College of Cardiology 40(2): 298-303.

Chan W, Ivanov J, Ko D et al. (2015) Clinical outcomes of treatment by percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with chronic kidney disease undergoing index revascularization in Ontario. Circulation. Cardiovascular interventions 8(1).

Cho R, Javed N, Traub D et al. (2010) Oral hydration and alkalinization is noninferior to intravenous therapy for prevention of contrast-induced nephropathy in patients with chronic kidney disease. Journal of interventional cardiology 23(5): 460-466.

Commercial Medicines Unit. Drugs and pharmaceutical electronic market information tool (eMIT). Accessed at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Accessed May 2019].

Curtis L & Burns A. (2018). Unit cost of health and social care 2018. University of Kent, UK.

Dangas G, Iakovou I, Nikolsky E et al. (2005) Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. The American journal of cardiology 95(1): 13-19.

Department of Health and Social Care (2016). NHS reference costs 2015 to 2016. Accessed at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.

Eriksen BO and Ingebretsen OC (2006) The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney international 69(2): 375-382.

Hoste EA, Doom S, De Waele J et al. (2011) Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis. Intensive care medicine 37(12): 1921-1931.

Hussain JA; Mooney A; Russon L (2013) Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. Palliative medicine 27(9): 829-839.

James MT, Ghali WA, Knudtson ML et al. (2011) Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 123(4): 409-416.

James MT, Hemmelgarn BR, Wiebe N et al. (2010) Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet (London, England) 376(9758): 2096-2103.

Jesky MD, Dutton M, Dasgupta I et al. (2016) Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. PloS one 11(11): e0165675.

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed June 2019].

Jones-Hughes T, Snowsill T, Haasova M et al. (2016) Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model. Health technology assessment (Winchester, England) 20(62): 1-594.

Kaltenthaler E, Tappenden P, Paisley S, Squires H. (2011). NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Accessed at: http://www.nicedsu.org.uk.

Kama A, Yılmaz S, Yaka E et al. (2014) Comparison of short-term infusion regimens of N-acetylcysteine plus intravenous fluids, sodium bicarbonate plus intravenous fluids, and intravenous fluids alone for prevention of contrast-induced nephropathy in the emergency department. Academic emergency medicine: official journal of the Society for Academic Emergency Medicine 21(6): 615-622.

Kind P, Hardman G, Macran S. (1999) UK population norms for EQ-5D. CHE Discussion Paper 175, University of York, UK.

Liem YS; Bosch JL; Hunink MG (2008) Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 11(4): 733-741.

Maioli M, Toso A, Leoncini M et al. (2012) Persistent renal damage after contrast-induced acute kidney injury: incidence, evolution, risk factors, and prognosis. Circulation 125(25): 3099-3107.

Maioli M, Toso A, Leoncini M et al. (2008) Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Journal of the American College of Cardiology 52(8): 599-604.

Marks A, Black C, Fluck N et al. (2012) Translating chronic kidney disease epidemiology into patient care--the individual/public health risk paradox. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association: iii65.

Martin-Moreno PL, Varo N, Martínez-Ansó E et al. (2015) Comparison of Intravenous and Oral Hydration in the Prevention of Contrast-Induced Acute Kidney Injury in Low-Risk Patients: A Randomized Trial. Nephron 131(1): 51-58.

Mehran R, Aymong ED, Nikolsky E et al. (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. Journal of the American College of Cardiology 44(7): 1393-1399.

Mueller C, Buerkle G, Buettner HJ et al. (2002) Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Archives of internal medicine 162(3): 329-336.

NHS Blood and Transplant (2018). Organ Donation and Transplantation Activity Report 2017/18. Accessed at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets/1848/transplant-activity-report-2017-2018.pdf.

NHS Business Services Authority (2019a). Drug Tariff, June 2019. Accessed at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff.

NHS Business Services Authority (2019b). Prescription Cost Analysis (PCA) data, March 2019. https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data.

NHS Improvement (2018). National schedule of reference costs 2017-18. Accessed at: https://improvement.nhs.uk/resources/reference-costs/#rc1718.

NICE (2018). Renal replacement therapy and conservative management. NICE guideline [NG107].

NICE (2015). Chronic kidney disease: managing anaemia. NICE guideline [NG8].

NICE (2013a). Acute kidney injury: prevention, detection and management. NICE clinical guideline [CG169].

NICE (2013b). Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia. Clinical guideline [CG157].

Nisula S, Vaara ST, Kaukonen KM et al. (2013) Six-month survival and quality of life of intensive care patients with acute kidney injury. Critical care (London, England) 17(5): R250.

Office for National Statistics (2018). National life tables, UK: 2015-2017. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables.

Rashid ST, Salman M, Myint F et al. (2004) Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine. Journal of vascular surgery 40(6): 1136-1141.

Sadineni R, Karthik KR, Swarnalatha G et al. (2017) N-acetyl cysteine versus allopurinol in the prevention of contrast nephropathy in patients with chronic kidney disease: A randomized controlled trial. Indian journal of nephrology 27(2): 93-98.

Serruys PW, Morice MC, Kappetein AP et al. (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. The New England journal of medicine 360(10): 961-972.

UK Renal Registry (2018) 20th Annual Report of the Renal Association. Nephron 139 (suppl1).

Villar E, Remontet L, Labeeuw M et al. (2007) Effect of age, gender, and diabetes on excess death in end-stage renal failure. Journal of the American Society of Nephrology: JASN 18(7): 2125-2134.

Appendix M – Excluded studies

Clinical studies

Study	Reason
(2007) MEENA (A Randomized Controlled Trial for the Prevention of Contrast-induced Nephropathy with Sodium Bicarbonate in Persons Undergoing Coronary Angiography). Clinical Cardiology 30(8): 416-416	- Conference abstract
Agarwal, Shiv Kumar, Mohareb, Sameh, Patel, Achint et al. (2015) Systematic oral hydration with water is similar to parenteral hydration for prevention of contrast-induced nephropathy: an updated meta-analysis of randomised clinical data. Open heart 2(1): e000317	- More recent systematic review covers the same topic
Ahmed, K., McVeigh, T., Cerneviciute, R. et al. (2018) Effectiveness of contrast-associated acute kidney injury prevention methods; A systematic review and network meta-analysis. BMC Nephrology 19(1): 323	- Systematic review used as source of primary studies [Some of the interventions were not relevant for the update.]
Alessandri, N., Lanzi, L., Garante, C. M. et al. (2013) Prevention of acute renal failure post-contrast imaging in cardiology: a randomized study. European review for medical and pharmacological sciences 17suppl1: 13-21	- Not a relevant study design [Retrospective observational study]
Ali-Hasan-Al-Saegh, Sadeq, Mirhosseini, Seyed Jalil, Ghodratipour, Zahra et al. (2017) Strategies Preventing Contrast-Induced Nephropathy After Coronary Angiography: A Comprehensive Meta-Analysis and Systematic Review of 125 Randomized Controlled Trials. Angiology 68(5): 389-413	- More recent systematic review covers the same topic
Ali-Hassan-Sayegh, S., Mirhosseini, S. J., Rahimizadeh, E. et al. (2015) Current status of sodium bicarbonate in coronary angiography: An updated comprehensive meta-analysis and systematic review. Cardiology Research and Practice 2015: 690308	- More recent systematic review covers the same topic
Alonso, A., Lau, J., Jaber, B. L. et al. (2004) Prevention of Radiocontrast Nephropathy with N-Acetylcysteine in Patients with Chronic Kidney Disease: a Meta-Analysis of Randomized, Controlled Trials. American journal of kidney diseases 43(1): 1-9	- Does not contain a population of people at risk of CI-AKI
Alonso, Pau, Sanz, Jorge, Garcia-Orts, Ana et al. (2017) Usefulness of Sodium Bicarbonate for the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Cardiac Resynchronization Therapy. The American journal of cardiology 120(9): 1584-1588	- Does not contain a population of people at risk of CI-AKI
Bagshaw, S. M. and Ghali, W. A. (2004) Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. BMC medicine 2: 38	- More recent systematic review covers the same topic
Bailey, Michael, McGuinness, Shay, Haase, Michael et al. (2015) Sodium bicarbonate and renal function after cardiac surgery: a prospectively planned individual patient meta-analysis. Anesthesiology 122(2): 294-306	- More recent systematic review covers the same topic
Balderramo D, Verdu M, Ramacciotti. C.F. et al. (2004) Renoprotective 30 effect of high periprocedural doses of	- Does not contain a population of people at risk of CI-AKI

Study	Reason
oral N-acetylcysteine in patients scheduled to undergo a same-day angiography. Revista De La Facultad De Ciencias Medicas De Cordoba 61(2)	
Berwanger, Otavio, Cavalcanti, Alexandre Biasi, Sousa, Amanda M. G. et al. (2013) Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: a substudy of the acetylcysteine for contrast-induced nephropathy trial. Circulation. Cardiovascular interventions 6(2): 139-45	- Secondary publication of an included study that does not provide any additional relevant information
Biernacka-Fialkowska, Barbara, Szuksztul, Marta, Suslik, Wojciech et al. (2018) Intravenous N-acetylcysteine for the PRevention Of Contrast-induced nephropathy - a prospective, single-center, randomized, placebo-controlled trial. The INPROC trial. Postepy w kardiologii interwencyjnej = Advances in interventional cardiology 14(1): 59-66	- Does not contain a population of people at risk of CI-AKI
Boccalandro, F., Amhad, M., Smalling, R. W. et al. (2003) Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheterization and cardiovascular interventions 58(3): 336-341	- Not a relevant study design
Brown, Jeremiah R., Pearlman, Daniel M., Marshall, Emily J. et al. (2016) Meta-Analysis of Individual Patient Data of Sodium Bicarbonate and Sodium Chloride for All-Cause Mortality After Coronary Angiography. The American journal of cardiology 118(10): 1473-1479	- More recent systematic review covers the same topic
Brueck, Martin, Cengiz, Huelya, Hoeltgen, Reinhard et al. (2013) Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. The Journal of invasive cardiology 25(6): 276-83	- Does not contain a population of people at risk of CI-AKI
Burns KE; Priestap F; Martin C (2010) N-acetylcysteine in critically ill patients undergoing contrast-enhanced computed tomography: a randomized trial.. Clinical nephrology 74(4): 323-326	- Letter to editor
Busch, Sarah Victoria Ekelof, Jensen, Svend Eggert, Rosenberg, Jacob et al. (2013) Prevention of contrast-induced nephropathy in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review. Journal of interventional cardiology 26(1): 97-105	- More recent systematic review covers the same topic
Chen, H. W., Zhang, J. J., Xiong, D. et al. (2016) Prevention and Treatment of Shenkang Injection for Contrast-induced Nephropathy in Elder Patients with Chronic Kidney Disease. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine 36(7): 792-796	- Study not reported in English [Chinese]
Cheungpasitporn, Wisit, Thongprayoon, Charat, Brabec, Brady A. et al. (2014) Oral hydration for prevention of	- More recent systematic review covers the same topic

Study	Reason
contrast-induced acute kidney injury in elective radiological procedures: a systematic review and meta-analysis of randomized controlled trials. North American journal of medical sciences 6(12): 618-24	
Dabare, Dilan, Banihani, Mohammed, Gibbs, Paul et al. (2013) Does bicarbonate prevent contrast-induced nephropathy in cardiovascular patients undergoing contrast imaging?. Interactive cardiovascular and thoracic surgery 17(6): 1028-35	- More recent systematic review covers the same topic
Ding, L.; Zhuang, G. H.; Ding, B. (2016) Clinical application of intravenous hydration or oral hydration in preventing contrast-induced nephropathy in patients with cardiac insufficiency. Journal of interventional radiology (china) 25(1): 15-18	- Study not reported in English [Chinese]
Dong, Yuhao, Zhang, Bin, Liang, Long et al. (2016) How Strong Is the Evidence for Sodium Bicarbonate to Prevent Contrast-Induced Acute Kidney Injury After Coronary Angiography and Percutaneous Coronary Intervention?. Medicine 95(7): e2715	- More recent systematic review covers the same topic
Eskandarian, R., Yarmohamadi, M., Zaker-Tavalae, M. et al. (2018) The standard dose versus double dose of n-acetylcysteine to prevent contrast-induced nephropathy; a randomized controlled clinical trial. Journal of Nephropathology 7(3): 145-150	- Data not reported in an extractable format
Giacoppo, Daniele, Gargiulo, Giuseppe, Buccheri, Sergio et al. (2017) Preventive Strategies for Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Procedures: Evidence From a Hierarchical Bayesian Network Meta-Analysis of 124 Trials and 28 240 Patients. Circulation. Cardiovascular interventions 10(5)	- Systematic review used as source of primary studies [Some of the interventions were not relevant for the update. The NMA was only for patients undergoing percutaneous coronary procedures.]
Glaza, M.; Rutkowski, B.; Szolkiewicz, M. (2018) Prevention of contrast-induced nephropathy in patients after percutaneous coronary intervention: A single-center prospective study. Clinical Nephrology 90(5): 370-372	- Letter to editor [About PRESERVE trial]
Guru, V. and Fremes, S. E. (2004) The role of N-acetylcysteine in preventing radiographic contrast-induced nephropathy. Clinical nephrology 62(2): 77-83	- More recent systematic review covers the same topic
Heguilen, Ricardo M., Liste, Amador A., Payaslian, Miguel et al. (2013) N-acethyl-cysteine reduces the occurrence of contrast-induced acute kidney injury in patients with renal dysfunction: a single-center randomized controlled trial. Clinical and experimental nephrology 17(3): 396-404	- Does not contain a population of people at risk of CI-AKI
Hiremath, Swapnil, Akbari, Ayub, Shabana, Wael et al. (2013) Prevention of contrast-induced acute kidney injury: is simple oral hydration similar to intravenous? A systematic review of the evidence. PloS one 8(3): e60009	- More recent systematic review covers the same topic
Inda-Filho, Antonio Jose, Caixeta, Adriano, Manggini, Marcia et al. (2014) Do intravenous N-acetylcysteine	- Does not contain a population of people at risk of CI-AKI

Study	Reason
and sodium bicarbonate prevent high osmolal contrast-induced acute kidney injury? A randomized controlled trial. PloS one 9(9): e107602	
Izcovich, Ariel and Rada, Gabriel (2015) Should acetylcysteine be used to prevent contrast induced nephropathy?. Medwave 15(3): e6122	- More recent systematic review covers the same topic
Jang, Jae-Sik, Jin, Han-Young, Seo, Jeong-Sook et al. (2012) Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury - a systematic review and meta-analysis. Circulation journal : official journal of the Japanese Circulation Society 76(9): 2255-65	- More recent systematic review covers the same topic
Jiang, Yufeng, Chen, Min, Zhang, Yiqing et al. (2017) Meta-analysis of prophylactic hydration versus no hydration on contrast-induced acute kidney injury. Coronary artery disease 28(8): 649-657	- More recent systematic review covers the same topic
Jurado-Roman, Alfonso, Hernandez-Hernandez, Felipe, Garcia-Tejada, Julio et al. (2015) Role of hydration in contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. The American journal of cardiology 115(9): 1174-8	- Does not contain a population of people at risk of CI-AKI
Kanbay, M., Covic, A., Coca, S. G. et al. (2009) Sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of 17 randomized trials. International urology and nephrology 41(3): 617-627	- More recent systematic review covers the same topic
Kang, Xin, Hu, Da-Yong, Li, Chang-Bin et al. (2015) N-acetylcysteine for the prevention of contrast-induced nephropathy in patients with pre-existing renal insufficiency or diabetes: a systematic review and meta-analysis. Renal failure 37(10): 297-303	- More recent systematic review covers the same topic
Khaledifar, A., Momeni, A., Ebrahimi, A. et al. (2015) Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy. ARYA Atherosclerosis 11(4)	- Ocurrence of contrast induced AKI was not reported
Khan, Safi U., Khan, Muhammad U., Rahman, Hammad et al. (2019) A Bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization. Cardiovascular revascularization medicine : including molecular interventions 20(1): 29-37	- Systematic review used as source of primary studies [Some of the interventions were not relevant for the update.]
Kim, Byung Jin, Sung, Ki Chul, Kim, Bum Soo et al. (2010) Effect of N-Acetylcysteine on cystatin C-Based renaL function after Elective coronary angiography (ENABLE Study): A prospective, randomized trial. International Journal of Cardiology 138(3): 239-245	- Does not contain a population of people at risk of CI-AKI
Kimmel, Martin, Butscheid, Moritz, Brenner, Stefanie et al. (2008) Improved estimation of glomerular filtration rate by serum cystatin C in preventing contrast induced nephropathy by N -acetylcysteine or zinc?preliminary results. ndt 23(4): 1241-1245	- Study was halted before it finished recruiting
Koc, Fatih, Ozdemir, Kurtulus, Altunkas, Fatih et al. (2013) Sodium bicarbonate versus isotonic saline for the	- Does not contain a population of people at risk of CI-AKI

Study	Reason
prevention of contrast-induced nephropathy in patients with diabetes mellitus undergoing coronary angiography and/or intervention: a multicenter prospective randomized study. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 61(5): 872-7	
Kumar, A., Bhawani, G., Kumari, N. et al. (2014) Comparative study of renal protective effects of allopurinol and n-acetyl-cysteine on contrast induced nephropathy in patients undergoing cardiac catheterization. Journal of Clinical and Diagnostic Research 8(12): HC03-HC07	- Does not contain a population of people at risk of CI-AKI
Li, J., Jin, E., Yu, L. et al. (2017) Oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients following coronary angioplasty: A meta-analysis. Experimental and Therapeutic Medicine 14(2): 1568-1576	- More recent systematic review covers the same topic
Liu, R., Nair, D., Ix, J. et al. (2005) N-acetylcysteine for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Journal of General Internal Medicine 20(2): 193-200	- More recent systematic review covers the same topic
Loomba, R. S., Shah, P. H., Aggarwal, S. et al. (2013) Role of N-acetylcysteine to prevent contrast-induced nephropathy: a meta-analysis. American Journal of Therapeutics: epub	- More recent systematic review covers the same topic
Loomba, Rohit S., Shah, Parinda H., Aggarwal, Saurabh et al. (2016) Role of N-Acetylcysteine to Prevent Contrast-Induced Nephropathy: A Meta-analysis. American journal of therapeutics 23(1): e172-83	- More recent systematic review covers the same topic
Luo, Yu, Wang, Xiaodong, Ye, Zi et al. (2014) Remedial hydration reduces the incidence of contrast-induced nephropathy and short-term adverse events in patients with ST-segment elevation myocardial infarction: a single-center, randomized trial. Internal medicine (Tokyo, Japan) 53(20): 2265-72	- Does not contain a population of people at risk of CI-AKI
Ma, W. Q., Zhao, Y., Wang, Y. et al. (2018) Comparative efficacy of pharmacological interventions for contrast-induced nephropathy prevention after coronary angiography: a network meta-analysis from randomized trials. International Urology and Nephrology 50(6): 1085-1095	- Systematic review used as source of primary studies [Some of the interventions were not relevant for the update.]
Mahmoodi, Khalil, Sohrabi, Bahram, Ilkhchooyi, Farzad et al. (2014) The Efficacy of Hydration with Normal Saline Versus Hydration with Sodium Bicarbonate in the Prevention of Contrast-induced Nephropathy. Heart views : the official journal of the Gulf Heart Association 15(2): 33-6	- Does not contain a population of people at risk of CI-AKI
Manari, Antonio, Magnavacchi, Paolo, Puggioni, Enrico et al. (2014) Acute kidney injury after primary angioplasty: effect of different hydration treatments. Journal of cardiovascular medicine (Hagerstown, Md.) 15(1): 60-7	- Does not contain a population of people at risk of CI-AKI

Study	Reason
Navarese, Eliano P., Gurbel, Paul A., Andreotti, Felicita et al. (2017) Prevention of contrast-induced acute kidney injury in patients undergoing cardiovascular procedures-a systematic review and network meta-analysis. PloS one 12(2): e0168726	- Systematic review used as source of primary studies [Some interventions were not relevant for this update. The NMA was only for patients undergoing cardiovascular procedures.]
O'Sullivan, S., Healy, D. A., Moloney, Mary Clarke et al. (2013) The role of N--acetylcysteine in the prevention of contrast-induced nephropathy in patients undergoing peripheral angiography: a structured review and meta-analysis. Angiology 64(8): 576-82	- More recent systematic review covers the same topic
Pakfetrat M, Nikoo MH, Malekmakan L et al. (2009) A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial.. International urology and nephrology 41(3): 629-634	- Does not contain a population of people at risk of CI-AKI
Pakfetrat, Maryam, Malekmakan, Leila, Salmanpour, Zahra et al. (2019) Comparison of Normal Saline, Ringer's Lactate, and Sodium Bicarbonate for Prevention of Contrast-induced Nephropathy in Patients with Coronary Angiography: A Randomized Double-blind Clinical Trial. Indian journal of nephrology 29(1): 22-27	- Does not contain a population of people at risk of CI-AKI
Pandya, B., Chaloub, J., Parikh, V. et al. (2017) Contrast media use in patients with chronic kidney disease undergoing coronary angiography: A systematic review and meta-analysis of randomized trials. International Journal of Cardiology 228: 137-144	- More recent systematic review covers the same topic
Pezeshgi, Aiyoub, Parsamanesh, Negin, Farhood, Goodarz et al. (2015) Evaluation of the protective effect of N-acetylcysteine on contrast media nephropathy. Journal of renal injury prevention 4(4): 109-12	- Does not contain a population of people at risk of CI-AKI
Poletti, Pierre-Alexandre, Platon, Alexandra, De Seigneux, Sophie et al. (2013) N-acetylcysteine does not prevent contrast nephropathy in patients with renal impairment undergoing emergency CT: a randomized study. BMC nephrology 14: 119	- Data not reported in an extractable format [Ocurrence of CI-AKI <5 days was not reported]
Ratcliffe JA, Thiagarajah P, Chen J et al. (2009) Prevention of contrast-induced nephropathy: A randomized controlled trial of sodium bicarbonate and N-acetylcysteine.. The International journal of angiology : official publication of the International College of Angiology, Inc 18(4): 193-197	- Does not contain a population of people at risk of CI-AKI
Sadat U, Walsh SR, Norden AG et al. (2011) Does oral N-acetylcysteine reduce contrast-induced renal injury in patients with peripheral arterial disease undergoing peripheral angiography? A randomized-controlled study.. Angiology 62(3): 225-230	- Does not contain a population of people at risk of CI-AKI
Sar F, Saler T, Ecebay A et al. (2010) The efficacy of n-acetylcysteine in preventing contrast-induced nephropathy in type 2 diabetic patients without nephropathy.. Journal of nephrology 23(4): 478-482	- Does not contain a population of people at risk of CI-AKI

Study	Reason
Sharp, Alexander J., Patel, Nishith, Reeves, Barney C. et al. (2019) Pharmacological interventions for the prevention of contrast-induced acute kidney injury in high-risk adult patients undergoing coronary angiography: a systematic review and meta-analysis of randomised controlled trials. Open heart 6(1): e000864	- More recent systematic review covers the same topic
Silva RG, Silva NG, Lucchesi F et al. (2010) Prevention of contrast-induced nephropathy by use of bicarbonate solution: preliminary results and literature review.. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia 32(3): 292-302	- Data not reported in an extractable format [number of pts per group not reported (results [preliminary] reported on pages 293-294)]
Sinert, R. and Doty, C. I. (2009) Update: prevention of contrast-induced nephropathy in the emergency department. Annals of Emergency Medicine 54(1): e1-e5	- More recent systematic review covers the same topic
Su, Xiaole, Xie, Xinfang, Liu, Lijun et al. (2017) Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 69(1): 69-77	- Systematic review used as source of primary studies [Some of the interventions are not relevant for this update.]
Subramaniam, Rathan M., Suarez-Cuervo, Catalina, Wilson, Renee F. et al. (2016) Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. Annals of internal medicine 164(6): 406-16	- More recent systematic review covers the same topic
Subramaniam, Rathan M., Wilson, Renee F., Turban, Sharon et al. (2016) Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures. Agency for Healthcare Research and Quality (US). AHRQ Comparative Effectiveness Reviews, Report No.: 15(16)-EHC023-EF	- More recent systematic review covers the same topic
Sun, Zikai, Fu, Qiang, Cao, Longxing et al. (2013) Intravenous N-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. PloS one 8(1): e55124	- More recent systematic review covers the same topic
Tanaka A, Suzuki Y, Suzuki N et al. (2011) Does N-acetylcysteine reduce the incidence of contrast-induced nephropathy and clinical events in patients undergoing primary angioplasty for acute myocardial infarction?. Internal medicine (Tokyo, Japan) 50(7): 673-677	- Does not contain a population of people at risk of CI-AKI
Thayssen, Per, Lassen, Jens Flensted, Jensen, Svend Eggert et al. (2014) Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. Circulation. Cardiovascular interventions 7(2): 216-24	- Does not contain a population of people at risk of CI-AKI
Trivedi HS, Moore H, Nasr S et al. (2003) A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity.. Nephron. Clinical practice 93(1): c29	- Does not contain a population of people at risk of CI-AKI

Study	Reason
Valette, Xavier, Desmeulles, Isabelle, Savary, Benoit et al. (2017) Sodium Bicarbonate Versus Sodium Chloride for Preventing Contrast-Associated Acute Kidney Injury in Critically Ill Patients: A Randomized Controlled Trial. Critical care medicine 45(4): 637-644	- Does not contain a population of people at risk of CI-AKI
Wang, Nelson, Qian, Pierre, Kumar, Shejil et al. (2016) The effect of N-acetylcysteine on the incidence of contrast-induced kidney injury: A systematic review and trial sequential analysis. International journal of cardiology 209: 319-27	- More recent systematic review covers the same topic
Weisbord, Steven D., Gallagher, Martin, Kaufman, James et al. (2013) Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. Clinical journal of the American Society of Nephrology : CJASN 8(9): 1618-31	- More recent systematic review covers the same topic
Wu, Mei-Yi, Hsiang, Hui-Fen, Wong, Chung-Shun et al. (2013) The effectiveness of N-Acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials. International urology and nephrology 45(5): 1309-18	- More recent systematic review covers the same topic
Xu, Renfan, Tao, Anyu, Bai, Yang et al. (2016) Effectiveness of N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association 5(9)	- More recent systematic review covers the same topic
Yang, Kun, Liu, Wenxian, Ren, Wei et al. (2014) Different interventions in preventing contrast-induced nephropathy after percutaneous coronary intervention. International urology and nephrology 46(9): 1801-7	- Does not contain a population of people at risk of CI-AKI
Yeganehkhah, Mohammad Reza, Iranirad, Leili, Dorri, Farshad et al. (2014) Comparison between three supportive treatments for prevention of contrast-induced nephropathy in high-risk patients undergoing coronary angiography. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 25(6): 1217-23	- Data not reported in an extractable format [Figure 1 and data reported in text (page 1219) don't match]
Zagler, Axel, Azadpour, Maziar, Mercado, Carlos et al. (2006) N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. American heart journal 151(1): 140-5	- More recent systematic review covers the same topic
Zapata-Chica, Carlos Andres, Bello Marquez, Diana, Serna-Higuita, Lina Maria et al. (2015) Sodium bicarbonate versus isotonic saline solution to prevent contrast-induced nephropathy : a systematic review and meta-analysis. Colombia medica (Cali, Colombia) 46(3): 90-103	- More recent systematic review covers the same topic
Zhang, Bin, Liang, Long, Chen, Wenbo et al. (2015) The efficacy of sodium bicarbonate in preventing contrast-induced nephropathy in patients with pre-existing renal insufficiency: a meta-analysis. BMJ open 5(3): e006989	- More recent systematic review covers the same topic

Study	Reason
Zhao, Shi-Jie, Zhong, Zhao-Shuang, Qi, Guo-Xian et al. (2016) The efficacy of N-acetylcysteine plus sodium bicarbonate in the prevention of contrast-induced nephropathy after cardiac catheterization and percutaneous coronary intervention: A meta-analysis of randomized controlled trials. International journal of cardiology 221: 251-9	- More recent systematic review covers the same topic
Zoungas, S., Ninomiya, T., Huxley, R. et al. (2009) Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Annals of internal medicine 151(9): 631-638	- More recent systematic review covers the same topic

Economic studies

Study	Reason
Kooiman, de Vries, Van der Heyden, Sijpkens, van Dijkman, Wever et al. (2018) Randomized trial of one-hour sodium bicarbonate vs standard periprocedural saline hydration in chronic kidney disease patients undergoing cardiovascular contrast procedures. PloS one 13(2): e0189372.	Does not include quality of life data.
Kooiman, Sijpkens, de Vries, Brulez, Hamming, van der Molen et al. (2014) A randomized comparison of 1-h sodium bicarbonate hydration versus standard peri-procedural saline hydration in patients with chronic kidney disease undergoing intravenous contrast-enhanced computerized tomography. European Renal Association 29(5); 1029-36.	Does not include quality of life data.
Kotlyar, Keogh, Thavapalachandran, Allada, Sharp, Dias et al. (2005) Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures--a randomised controlled trial. Heart, lung & circulation 14(4); 245-51.	Not an economic evaluation.
Nijssen, Rennenberg, Nelemans, Essers, Janssen, Vermeeren et al. (2017) Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet 389: 1312-22	Does not include quality of life data.

Appendix N – Research recommendations

Research recommendation 1

Potential criterion	Explanation
Importance to patients, service users or the population	An eGFR <40 ml/min/1.73 m^2 is associated with an increased risk of CI-AKI but the committee discussed that the risk might be different at other eGFR thresholds. The included RCTs in this update did not report any data on different eGFR thresholds. Therefore, the committee recommended that further research is needed to find out what eGFR thresholds are related to the risk of contrast-induced acute kidney injury.
Relevance to NICE guidance	Low-priority: it was possible to make recommendations based on the available evidence, but new evidence in this area has the potential to alter the recommendations substantially.
Current evidence base	The included RCTs in this update did not report any data on different eGFR thresholds.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	The committee noted that it might not be possible to do this research on people with very low eGFRs because they may be too high risk to be included in research studies. However, it agreed that better evidence of risk stratification for CI-AKI in people with higher eGFRs would still improve clinical practice and patient safety

Question	Can risk of contrast-induced acute kidney injury (CI-AKI) be stratified by eGFR thresholds?
Population	Adults (18 and older) who are at risk (as defined by the study author) of contrast induced AKI.
Prognostic factor	eGFR thresholds
Outcomes	• Occurrence of contrast-induced acute kidney injury
Study design	Prospective cohort studies.

Research recommendation 2

Question	What is the relative effectiveness and cost effectiveness of different oral fluids and different oral fluid regimes, both with and without oral NAC, at preventing CI-AKI?
Population	Adults (18 and older) who are at risk (as defined by the study author) of contrast induced AKI who are having oral rather than IV hydration to prevent CI-AKI.
Intervention	Different oral hydration regimes and agents, with or without NAC, including

Potential criterion	Explanation
Importance to patients, service users or the population	The committee agreed that oral hydration regimes were non-inferior to IV hydration regimes at preventing CI-AKI, however there was not enough comparative data to enable them to be clear about which oral fluid (if any) was most effective. They noted that it might not be possible to do this research on people with very low eGFRs because they may be too high risk to be included in research studies.
Relevance to NICE guidance	Low-priority: it was possible to make recommendations based on the available evidence, but new evidence in this area has the potential to alter the recommendations substantially.
Current evidence base	Only one study was identified that partly addressed this research question comparting oral fluids +bicarbonate to oral fluids alone (Cho, 2010).
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	No feasibility concerns were identified.
Study design	Randomised controlled trials
Question	**What is the relative effectiveness and cost effectiveness of different oral fluids and different oral fluid regimes, both with and without oral NAC, at preventing CI-AKI?**
	• Water • Sodium bicarbonate • Sodium citrate
Comparator	Each other or no oral or hydration
Outcomes	• Occurrence of contrast-induced acute kidney injury (within 72 hours of contrast administration)

Appendix O – References

Clinical studies

Included studies

Adolph, Esther, Holdt-Lehmann, Birgit, Chatterjee, Tushar et al. (2008) Renal Insufficiency Following Radiocontrast Exposure Trial (REINFORCE): a randomized comparison of sodium bicarbonate versus sodium chloride hydration for the prevention of contrast-induced nephropathy. Coronary artery disease 19(6): 413-9

Agrawal, M., Wodlinger, A.M., Huggins, C.E. et al. (2004) Effect of N-Acetylcysteine on Serum Creatinine Concentration in Patients with Chronic Renal Insufficiency Who Are Undergoing Coronary Angiography. Heart Drug 4(2): 87-91

Akyuz, Sukru, Karaca, Mehmet, Kemaloglu Oz, Tugba et al. (2014) Efficacy of oral hydration in the prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography or intervention. Nephron. Clinical practice 128(12): 95-100

Albabtain, Monirah A., Almasood, Ali, Alshurafah, Hytham et al. (2013) Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-Induced nephropathy: a prospective randomized study. Journal of interventional cardiology 26(1): 90-6

Allaqaband S, Tumuluri R, Malik AM et al. (2002) Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy.. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 57(3): 279-283

Aslanger, E., Uslu, B., Akdeniz, C. et al. (2012) Intrarenal application of N-acetylcysteine for the prevention of contrast medium-induced nephropathy in primary angioplasty. Coronary artery disease 23(4): 265-270

Baskurt, M., Okcun, B., Abaci, O. et al. (2009) N-acetylcysteine versus N-acetylcysteine + theophylline for the prevention of contrast nephropathy. European Journal of Clinical Investigation 39(9): 793-799

Berwanger, O. (2011) Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized acetylcysteine for contrast-induced nephropathy trial (ACT). Circulation 124(11): 1250-1259

Boucek, Petr, Havrdova, Terezia, Oliyarnyk, Olena et al. (2013) Prevention of contrast-induced nephropathy in diabetic patients with impaired renal function: a randomized, double blind trial of sodium bicarbonate versus sodium chloride-based hydration. Diabetes research and clinical practice 101(3): 303-8

Brar SS, Shen AY, Jorgensen MB et al. (2008) Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial.. JAMA 300(9): 1038-1046

Briguori C, Airoldi F, D'Andrea D et al. (2007) Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies.. Circulation 115(10): 1211-1217

Briguori C, Manganelli F, Scarpato P et al. (2002) Acetylcysteine and contrast agent-associated nephrotoxicity.. Journal of the American College of Cardiology 40(2): 298-303

Caglar, I. M., Caglar, F. N. T., Conkbayir, C. et al. (2014) Contrast study: Comparision of nephroprotective three protocols: Acetylcysteine-sodium bicarbonate-theophylline, to prevent contrast-induced nephropathy. Russian Journal of Cardiology 105(1): 27-31

Carbonell N, Sanjuán R, Blasco M et al. (2010) N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients.. Revista espanola de cardiologia 63(1): 12-19

Carbonell, Nieves, Blasco, Marisa, Sanjuán, Rafael et al. (2007) Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: A randomised trial. International Journal of Cardiology 115(1): 57-62

Castini, Diego, Lucreziotti, Stefano, Bosotti, Laura et al. (2010) Prevention of Contrast-induced Nephropathy: A Single Center Randomized Study. Clinical Cardiology 33(3): e63-e68

Chen, Shao Liang, Zhang, Junjie, Yei, Fei et al. (2008) Clinical outcomes of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention: a prospective, multicenter, randomized study to analyze the effect of hydration and acetylcysteine. International journal of cardiology 126(3): 407-13

Cho R, Javed N, Traub D et al. (2010) Oral hydration and alkalinization is noninferior to intravenous therapy for prevention of contrast-induced nephropathy in patients with chronic kidney disease.. Journal of interventional cardiology 23(5): 460-466

Chong, E., Poh, K. K., Lu, Q. et al. (2015) Comparison of combination therapy of high-dose oral N-acetylcysteine and intravenous sodium bicarbonate hydration with individual therapies in the reduction of Contrast-induced Nephropathy during Cardiac Catheterisation and Percutaneous Coronary Intervention (CONTRAST): A multi-centre, randomised, controlled trial. International Journal of Cardiology 201: 237-242

Durham JD, Caputo C, Dokko J et al. (2002) A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography.. Kidney international 62(6): 2202-2207

Erturk, Mehmet, Uslu, Nevzat, Gorgulu, Sevket et al. (2014) Does intravenous or oral high-dose N-acetylcysteine in addition to saline prevent contrast-induced nephropathy assessed by cystatin C?. Coronary artery disease 25(2): 111-7

Ferrario, Francesca, Barone, Maria Teresa, Landoni, Giovanni et al. (2009) Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy?a randomized controlled study. ndt 24(10): 3103-3107

Fung JW, Szeto CC, Chan WW et al. (2004) Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial.. American journal of kidney diseases : the official journal of the National Kidney Foundation 43(5): 801-808

Goldenberg I, Shechter M, Matetzky S et al. (2004) Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature.. European heart journal 25(3): 212-218

Gomes, V O, Poli de Figueredo, C E, Caramori, P et al. (2005) N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial. Heart 91(6): 774

Habib, Mohammed; Hillis, Alaa; Hammad, Amen (2016) N-acetylcysteine and/or ascorbic acid versus placebo to prevent contrast-induced nephropathy in patients undergoing elective cardiac catheterization: The NAPCIN trial; A single-center, prospective, randomized trial. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 27(1): 55-61

Hafiz, Abdul Moiz, Jan, M. Fuad, Mori, Naoyo et al. (2012) Prevention of contrast-induced acute kidney injury in patients with stable chronic renal disease undergoing elective percutaneous coronary and peripheral interventions: randomized comparison of two preventive strategies. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 79(6): 929-37

Heng AE, Cellarier E, Aublet-Cuvelier B et al. (2008) Is treatment with N-acetylcysteine to prevent contrast-induced nephropathy when using bicarbonate hydration out of date?. Clinical nephrology 70(6): 475-484

Hsu C, Lee J, Lo P et al. (2007) Prevention of radiocontrast-induced nephropathy with N-acetylcysteine after cardiac angiography in diabetic patients with renal dysfunction. Mid-Taiwan Journal of Medicine 12(4)

Izani Wan Mohamed W and Darus, Z: Yusof Z (2008) Oral N-acetylcysteine in prevention of contrast induced nephropathy following coronary angiogram. International Medical Journal 15(5): 353-361

Jaffery, Z., Verma, A., White, C. J. et al. (2012) A randomized trial of intravenous n-acetylcysteine to prevent contrast induced nephropathy in acute coronary syndromes. Catheterization and cardiovascular interventions 79(6): 921-926

Kama, Ahmet, Yilmaz, Serkan, Yaka, Elif et al. (2014) Comparison of short-term infusion regimens of N-acetylcysteine plus intravenous fluids, sodium bicarbonate plus intravenous fluids, and intravenous fluids alone for prevention of contrast-induced nephropathy in the emergency department. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 21(6): 615-22

Kay J, Chow WH, Chan TM et al. (2003) Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial.. JAMA 289(5): 553-558

Khalili H, Dashti-Khavidaki S, Tabifar H et al. (2006) N-acetylcysteine in the prevention of contrast agent-induced nephrotoxicity in patients undergoing computed tomography studies. Therapy 3(6)

Kitzler TM, Jaberi A, Sendlhofer G et al. (2012) Efficacy of vitamin E and N-acetylcysteine in the prevention of contrast induced kidney injury in patients with chronic kidney disease: a double blind, randomized controlled trial.. Wiener klinische Wochenschrift 124(910): 312-319

Koc, Fatih, Ozdemir, Kurtulus, Kaya, Mehmet Gungor et al. (2012) Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS--a multicenter prospective controlled trial. International journal of cardiology 155(3): 418-23

Kooiman, J., Sijpkens, Y. W. J., van Buren, M. et al. (2014) Randomised trial of no hydration vs. sodium bicarbonate hydration in patients with chronic kidney disease undergoing acute computed tomography-pulmonary angiography. Journal of thrombosis and haemostasis : JTH 12(10): 1658-66

Kooiman, Judith, de Vries, Jean-Paul P. M., Van der Heyden, Jan et al. (2018) Randomized trial of one-hour sodium bicarbonate vs standard periprocedural saline hydration in chronic kidney disease patients undergoing cardiovascular contrast procedures. PloS one 13(2): e0189372

Kooiman, Judith, Sijpkens, Yvo W. J., de Vries, Jean-Paul P. M. et al. (2014) A randomized comparison of 1-h sodium bicarbonate hydration versus standard peri-procedural saline hydration in patients with chronic kidney disease undergoing intravenous contrast-enhanced computerized tomography. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 29(5): 1029-36

Kotlyar E, Keogh AM, Thavapalachandran S et al. (2005) Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures--a randomised controlled trial.. Heart, lung & circulation 14(4): 245-251

Lee, Seung-Whan, Kim, Won-Jang, Kim, Young-Hak et al. (2011) Preventive Strategies of Renal Insufficiency in Patients With Diabetes Undergoing Intervention or Arteriography (the PREVENT Trial). The American Journal of Cardiology 107(10): 1447-1452

MacNeill, Briain D., Harding, Scott A., Bazari, Hasan et al. (2003) Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. Catheterization and Cardiovascular Interventions 60(4): 458-461

Maioli, Mauro, Toso, Anna, Leoncini, Mario et al. (2008) Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention. Journal of the American College of Cardiology 52(8): 599

Maioli, Mauro, Toso, Anna, Leoncini, Mario et al. (2011) Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial. Circulation. Cardiovascular interventions 4(5): 456-62

Marenzi G, Assanelli E, Marana I et al. (2006) N-acetylcysteine and contrast-induced nephropathy in primary angioplasty.. The New England journal of medicine 354(26): 2773-2782

Martin-Moreno, Paloma L., Varo, Nerea, Martinez-Anso, Eduardo et al. (2015) Comparison of Intravenous and Oral Hydration in the Prevention of Contrast-Induced Acute Kidney Injury in Low-Risk Patients: A Randomized Trial. Nephron 131(1): 51-8

Masuda M, Yamada T, Mine T et al. (2007) Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure.. The American journal of cardiology 100(5): 781-786

Masuda M, Yamada T, Okuyama Y et al. (2008) Sodium bicarbonate improves long-term clinical outcomes compared with sodium chloride in patients with chronic kidney disease undergoing an emergent coronary procedure.. Circulation journal : official journal of the Japanese Circulation Society 72(10): 1610-1614

Merten, Gregory J., Burgess, W. Patrick, Gray, Lee V. et al. (2004) Prevention of Contrast-Induced Nephropathy With Sodium BicarbonateA Randomized Controlled Trial. JAMA 291(19): 2328-2334

Miner, Steven E.S., Dzavik, Vladimir, Nguyen-Ho, Phong et al. (2004) N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. American Heart Journal 148(4): 690-695

Motohiro M, Kamihata H, Tsujimoto S et al. (2011) A new protocol using sodium bicarbonate for the prevention of contrast-induced nephropathy in patients undergoing coronary angiography.. The American journal of cardiology 107(11): 1604-1608

Mueller, Christian, Buerkle, Gerd, Buettner, Heinz J. et al. (2002) Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Archives of internal medicine 162(3): 329-36

Nieto-Rios, John Fredy, Salazar, Wilmar Arley Maya, Sanchez, Oscar Mauricio Santos et al. (2014) Prevention of contrast induced nephropathy with sodium bicarbonate (the PROMEC study). Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia 36(3): 360-6

Nijssen, Estelle C., Rennenberg, Roger J., Nelemans, Patty J. et al. (2017) Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet (London, England) 389(10076): 1312-1322

Oldemeyer, J.Bradley, Biddle, W.Paul, Wurdeman, Richard L et al. (2003) Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. American Heart Journal 146(6): 1089-1094

Poletti PA, Saudan P, Platon A et al. (2007) I.v. N-acetylcysteine and emergency CT: use of serum creatinine and cystatin C as markers of radiocontrast nephrotoxicity.. AJR. American journal of roentgenology 189(3): 687-692

Rashid ST, Salman M, Myint F et al. (2004) Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine.. Journal of vascular surgery 40(6): 1136-1141

Reinecke H, Fobker M, Wellmann J et al. (2007) A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) Trial.. Clinical research in cardiology : official journal of the German Cardiac Society 96(3): 130-139

Sadineni, R., Karthik, K. R., Swarnalatha, G. et al. (2017) N-acetyl cysteine versus allopurinol in the prevention of contrast nephropathy in patients with chronic kidney disease: A randomized controlled trial. Indian journal of nephrology 27(2): 93-98

Saitoh T, Satoh H, Nobuhara M et al. (2011) Intravenous glutathione prevents renal oxidative stress after coronary angiography more effectively than oral N-acetylcysteine.. Heart and vessels 26(5): 465-472

Seyon RA, Jensen LA, Ferguson IA et al. (2007) Efficacy of N-acetylcysteine and hydration versus placebo and hydration in decreasing contrast-induced renal dysfunction in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention.. Heart & lung : the journal of critical care 36(3): 195-204

Shyu KG; Cheng JJ; Kuan P (2002) Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure.. Journal of the American College of Cardiology 40(8): 1383-1388

Solomon, Richard, Gordon, Paul, Manoukian, Steven V. et al. (2015) Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD. Clinical journal of the American Society of Nephrology : CJASN 10(9): 1519-24

Tamura, Akira, Goto, Yukie, Miyamoto, Kumie et al. (2009) Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure. The American journal of cardiology 104(7): 921-5

Tepel M, van der Giet M, Schwarzfeld C et al. (2000) Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine.. The New England journal of medicine 343(3): 180-184

Thiele H, Hildebrand L, Schirdewahn C et al. (2010) Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial.. Journal of the American College of Cardiology 55(20): 2201-2209

Torigoe, Kumie, Tamura, Akira, Watanabe, Toru et al. (2013) 20-Hour preprocedural hydration is not superior to 5-hour preprocedural hydration in the prevention of contrast-induced increases in serum creatinine and cystatin C. International journal of cardiology 167(5): 2200-3

Traub, Stephen J., Mitchell, Alice M., Jones, Alan E. et al. (2013) N-acetylcysteine plus intravenous fluids versus intravenous fluids alone to prevent contrast-induced nephropathy in emergency computed tomography. Annals of emergency medicine 62(5): 511-520.e25

Turedi, Suleyman, Erdem, Erkan, Karaca, Yunus et al. (2016) The High Risk of Contrast-induced Nephropathy in Patients with Suspected Pulmonary Embolism Despite Three Different Prophylaxis: A Randomized Controlled Trial. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 23(10): 1136-1145

Ueda, Hiromichi, Yamada, Takahisa, Masuda, Masaharu et al. (2011) Prevention of Contrast-Induced Nephropathy by Bolus Injection of Sodium Bicarbonate in Patients With Chronic Kidney Disease Undergoing Emergent Coronary Procedures. The American Journal of Cardiology 107(8): 1163-1167

van Mourik, M. S., van Kesteren, F., Planken, R. N. et al. (2018) Short versus conventional hydration for prevention of kidney injury during pre-TAVI computed tomography angiography. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation 26(9): 425-432

Vasheghani-Farahani A, Sadigh G, Kassaian SE et al. (2010) Sodium bicarbonate in preventing contrast nephropathy in patients at risk for volume overload: a randomized controlled trial.. Journal of nephrology 23(2): 216-223

Webb JG, Pate GE, Humphries KH et al. (2004) A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect.. American heart journal 148(3): 422-429

Weisbord, Steven D., Gallagher, Martin, Jneid, Hani et al. (2018) Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. The New England journal of medicine 378(7): 603-614

Wrobel, Wojciech, Sinkiewicz, Wladyslaw, Gordon, Marcin et al. (2010) Oral versus intravenous hydration and renal function in diabetic patients undergoing percutaneous coronary interventions. Kardiologia polska 68(9): 1015-20

Excluded studies

(2007) MEENA (A Randomized Controlled Trial for the Prevention of Contrast-induced Nephropathy with Sodium Bicarbonate in Persons Undergoing Coronary Angiography). Clinical Cardiology 30(8): 416-416

Agarwal, Shiv Kumar, Mohareb, Sameh, Patel, Achint et al. (2015) Systematic oral hydration with water is similar to parenteral hydration for prevention of contrast-induced nephropathy: an updated meta-analysis of randomised clinical data. Open heart 2(1): e000317

Ahmed, K., McVeigh, T., Cerneviciute, R. et al. (2018) Effectiveness of contrast-associated acute kidney injury prevention methods; A systematic review and network meta-analysis. BMC Nephrology 19(1): 323

Alessandri, N., Lanzi, L., Garante, C. M. et al. (2013) Prevention of acute renal failure post-contrast imaging in cardiology: a randomized study. European review for medical and pharmacological sciences 17suppl1: 13-21

Ali-Hasan-Al-Saegh, Sadeq, Mirhosseini, Seyed Jalil, Ghodratipour, Zahra et al. (2017) Strategies Preventing Contrast-Induced Nephropathy After Coronary Angiography: A Comprehensive Meta-Analysis and Systematic Review of 125 Randomized Controlled Trials. Angiology 68(5): 389-413

Ali-Hassan-Sayegh, S., Mirhosseini, S. J., Rahimizadeh, E. et al. (2015) Current status of sodium bicarbonate in coronary angiography: An updated comprehensive meta-analysis and systematic review. Cardiology Research and Practice 2015: 690308

Alonso, A., Lau, J., Jaber, B. L. et al. (2004) Prevention of Radiocontrast Nephropathy with N-Acetylcysteine in Patients with Chronic Kidney Disease: a Meta-Analysis of Randomized, Controlled Trials. American journal of kidney diseases 43(1): 1-9

Alonso, Pau, Sanz, Jorge, Garcia-Orts, Ana et al. (2017) Usefulness of Sodium Bicarbonate for the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Cardiac Resynchronization Therapy. The American journal of cardiology 120(9): 1584-1588

Bagshaw, S. M. and Ghali, W. A. (2004) Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. BMC medicine 2: 38

Bailey, Michael, McGuinness, Shay, Haase, Michael et al. (2015) Sodium bicarbonate and renal function after cardiac surgery: a prospectively planned individual patient meta-analysis. Anesthesiology 122(2): 294-306

Balderramo D, Verdu M, Ramacciotti. C.F. et al. (2004) Renoprotective 30 effect of high periprocedural doses of oral N-acetylcysteine in patients scheduled to undergo a same-day angiography. Revista De La Facultad De Ciencias Medicas De Cordoba 61(2)

Berwanger, Otavio, Cavalcanti, Alexandre Biasi, Sousa, Amanda M. G. et al. (2013) Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: a substudy of the acetylcysteine for contrast-induced nephropathy trial. Circulation. Cardiovascular interventions 6(2): 139-45

Biernacka-Fialkowska, Barbara, Szuksztul, Marta, Suslik, Wojciech et al. (2018) Intravenous N-acetylcysteine for the PRevention Of Contrast-induced nephropathy - a prospective, single-center, randomized, placebo-controlled trial. The INPROC trial. Postepy w kardiologii interwencyjnej = Advances in interventional cardiology 14(1): 59-66

Boccalandro, F., Amhad, M., Smalling, R. W. et al. (2003) Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheterization and cardiovascular interventions 58(3): 336-341

Brown, Jeremiah R., Pearlman, Daniel M., Marshall, Emily J. et al. (2016) Meta-Analysis of Individual Patient Data of Sodium Bicarbonate and Sodium Chloride for All-Cause Mortality After Coronary Angiography. The American journal of cardiology 118(10): 1473-1479

Brueck, Martin, Cengiz, Huelya, Hoeltgen, Reinhard et al. (2013) Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. The Journal of invasive cardiology 25(6): 276-83

Burns KE; Priestap F; Martin C (2010) N-acetylcysteine in critically ill patients undergoing contrast-enhanced computed tomography: a randomized trial.. Clinical nephrology 74(4): 323-326

Busch, Sarah Victoria Ekelof, Jensen, Svend Eggert, Rosenberg, Jacob et al. (2013) Prevention of contrast-induced nephropathy in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review. Journal of interventional cardiology 26(1): 97-105

Chen, H. W., Zhang, J. J., Xiong, D. et al. (2016) Prevention and Treatment of Shenkang Injection for Contrast-induced Nephropathy in Elder Patients with Chronic Kidney Disease. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine 36(7): 792-796

Cheungpasitporn, Wisit, Thongprayoon, Charat, Brabec, Brady A. et al. (2014) Oral hydration for prevention of contrast-induced acute kidney injury in elective radiological procedures: a systematic review and meta-analysis of randomized controlled trials. North American journal of medical sciences 6(12): 618-24

Dabare, Dilan, Banihani, Mohammed, Gibbs, Paul et al. (2013) Does bicarbonate prevent contrast-induced nephropathy in cardiovascular patients undergoing contrast imaging?. Interactive cardiovascular and thoracic surgery 17(6): 1028-35

Ding, L.; Zhuang, G. H.; Ding, B. (2016) Clinical application of intravenous hydration or oral hydration in preventing contrast-induced nephropathy in patients with cardiac insufficiency. Journal of interventional radiology (china) 25(1): 15-18

Dong, Yuhao, Zhang, Bin, Liang, Long et al. (2016) How Strong Is the Evidence for Sodium Bicarbonate to Prevent Contrast-Induced Acute Kidney Injury After Coronary Angiography and Percutaneous Coronary Intervention?. Medicine 95(7): e2715

Eskandarian, R., Yarmohamadi, M., Zaker-Tavalae, M. et al. (2018) The standard dose versus double dose of n-acetylcysteine to prevent contrast-induced nephropathy; a randomized controlled clinical trial. Journal of Nephropathology 7(3): 145-150

Giacoppo, Daniele, Gargiulo, Giuseppe, Buccheri, Sergio et al. (2017) Preventive Strategies for Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Procedures: Evidence From a Hierarchical Bayesian Network Meta-Analysis of 124 Trials and 28 240 Patients. Circulation. Cardiovascular interventions 10(5)

Glaza, M.; Rutkowski, B.; Szolkiewicz, M. (2018) Prevention of contrast-induced nephropathy in patients after percutaneous coronary intervention: A single-center prospective study. Clinical Nephrology 90(5): 370-372

Guru, V. and Fremes, S. E. (2004) The role of N-acetylcysteine in preventing radiographic contrast-induced nephropathy. Clinical nephrology 62(2): 77-83

Heguilen, Ricardo M., Liste, Amador A., Payaslian, Miguel et al. (2013) N-acethyl-cysteine reduces the occurrence of contrast-induced acute kidney injury in patients with renal dysfunction: a single-center randomized controlled trial. Clinical and experimental nephrology 17(3): 396-404

Hiremath, Swapnil, Akbari, Ayub, Shabana, Wael et al. (2013) Prevention of contrast-induced acute kidney injury: is simple oral hydration similar to intravenous? A systematic review of the evidence. PloS one 8(3): e60009

Inda-Filho, Antonio Jose, Caixeta, Adriano, Manggini, Marcia et al. (2014) Do intravenous N-acetylcysteine and sodium bicarbonate prevent high osmolal contrast-induced acute kidney injury? A randomized controlled trial. PloS one 9(9): e107602

Izcovich, Ariel and Rada, Gabriel (2015) Should acetylcysteine be used to prevent contrast induced nephropathy?. Medwave 15(3): e6122

Jang, Jae-Sik, Jin, Han-Young, Seo, Jeong-Sook et al. (2012) Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury - a systematic review and meta-analysis. Circulation journal : official journal of the Japanese Circulation Society 76(9): 2255-65

Jiang, Yufeng, Chen, Min, Zhang, Yiqing et al. (2017) Meta-analysis of prophylactic hydration versus no hydration on contrast-induced acute kidney injury. Coronary artery disease 28(8): 649-657

Jurado-Roman, Alfonso, Hernandez-Hernandez, Felipe, Garcia-Tejada, Julio et al. (2015) Role of hydration in contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. The American journal of cardiology 115(9): 1174-8

Kanbay, M., Covic, A., Coca, S. G. et al. (2009) Sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of 17 randomized trials. International urology and nephrology 41(3): 617-627

Kang, Xin, Hu, Da-Yong, Li, Chang-Bin et al. (2015) N-acetylcysteine for the prevention of contrast-induced nephropathy in patients with pre-existing renal insufficiency or diabetes: a systematic review and meta-analysis. Renal failure 37(10): 297-303

Khaledifar, A., Momeni, A., Ebrahimi, A. et al. (2015) Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy. ARYA Atherosclerosis 11(4)

Khan, Safi U., Khan, Muhammad U., Rahman, Hammad et al. (2019) A Bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization. Cardiovascular revascularization medicine : including molecular interventions 20(1): 29-37

Kim, Byung Jin, Sung, Ki Chul, Kim, Bum Soo et al. (2010) Effect of N-Acetylcysteine on cystatin C-Based renaL function after Elective coronary angiography (ENABLE Study): A prospective, randomized trial. International Journal of Cardiology 138(3): 239-245

Kimmel, Martin, Butscheid, Moritz, Brenner, Stefanie et al. (2008) Improved estimation of glomerular filtration rate by serum cystatin C in preventing contrast induced nephropathy by N -acetylcysteine or zinc?preliminary results. ndt 23(4): 1241-1245

Koc, Fatih, Ozdemir, Kurtulus, Altunkas, Fatih et al. (2013) Sodium bicarbonate versus isotonic saline for the prevention of contrast-induced nephropathy in patients with diabetes mellitus undergoing coronary angiography and/or intervention: a multicenter prospective randomized study. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 61(5): 872-7

Kumar, A., Bhawani, G., Kumari, N. et al. (2014) Comparative study of renal protective effects of allopurinol and n-acetyl-cysteine on contrast induced nephropathy in patients undergoing cardiac catheterization. Journal of Clinical and Diagnostic Research 8(12): HC03-HC07

Li, J., Jin, E., Yu, L. et al. (2017) Oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients following coronary angioplasty: A meta-analysis. Experimental and Therapeutic Medicine 14(2): 1568-1576

Liu, R., Nair, D., Ix, J. et al. (2005) N-acetylcysteine for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Journal of General Internal Medicine 20(2): 193-200

Loomba, R. S., Shah, P. H., Aggarwal, S. et al. (2013) Role of N-acetylcysteine to prevent contrast-induced nephropathy: a meta-analysis. American Journal of Therapeutics: epub

Loomba, Rohit S., Shah, Parinda H., Aggarwal, Saurabh et al. (2016) Role of N-Acetylcysteine to Prevent Contrast-Induced Nephropathy: A Meta-analysis. American journal of therapeutics 23(1): e172-83

Luo, Yu, Wang, Xiaodong, Ye, Zi et al. (2014) Remedial hydration reduces the incidence of contrast-induced nephropathy and short-term adverse events in patients with ST-segment elevation myocardial infarction: a single-center, randomized trial. Internal medicine (Tokyo, Japan) 53(20): 2265-72

Ma, W. Q., Zhao, Y., Wang, Y. et al. (2018) Comparative efficacy of pharmacological interventions for contrast-induced nephropathy prevention after coronary angiography: a network meta-analysis from randomized trials. International Urology and Nephrology 50(6): 1085-1095

Mahmoodi, Khalil, Sohrabi, Bahram, Ilkhchooyi, Farzad et al. (2014) The Efficacy of Hydration with Normal Saline Versus Hydration with Sodium Bicarbonate in the Prevention of

Contrast-induced Nephropathy. Heart views : the official journal of the Gulf Heart Association 15(2): 33-6

Manari, Antonio, Magnavacchi, Paolo, Puggioni, Enrico et al. (2014) Acute kidney injury after primary angioplasty: effect of different hydration treatments. Journal of cardiovascular medicine (Hagerstown, Md.) 15(1): 60-7

Navarese, Eliano P., Gurbel, Paul A., Andreotti, Felicita et al. (2017) Prevention of contrast-induced acute kidney injury in patients undergoing cardiovascular procedures-a systematic review and network meta-analysis. PloS one 12(2): e0168726

O'Sullivan, S., Healy, D. A., Moloney, Mary Clarke et al. (2013) The role of N--acetylcysteine in the prevention of contrast-induced nephropathy in patients undergoing peripheral angiography: a structured review and meta-analysis. Angiology 64(8): 576-82

Pakfetrat M, Nikoo MH, Malekmakan L et al. (2009) A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial.. International urology and nephrology 41(3): 629-634

Pakfetrat, Maryam, Malekmakan, Leila, Salmanpour, Zahra et al. (2019) Comparison of Normal Saline, Ringer's Lactate, and Sodium Bicarbonate for Prevention of Contrast-induced Nephropathy in Patients with Coronary Angiography: A Randomized Double-blind Clinical Trial. Indian journal of nephrology 29(1): 22-27

Pandya, B., Chaloub, J., Parikh, V. et al. (2017) Contrast media use in patients with chronic kidney disease undergoing coronary angiography: A systematic review and meta-analysis of randomized trials. International Journal of Cardiology 228: 137-144

Pezeshgi, Aiyoub, Parsamanesh, Negin, Farhood, Goodarz et al. (2015) Evaluation of the protective effect of N-acetylcysteine on contrast media nephropathy. Journal of renal injury prevention 4(4): 109-12

Poletti, Pierre-Alexandre, Platon, Alexandra, De Seigneux, Sophie et al. (2013) N-acetylcysteine does not prevent contrast nephropathy in patients with renal impairment undergoing emergency CT: a randomized study. BMC nephrology 14: 119

Ratcliffe JA, Thiagarajah P, Chen J et al. (2009) Prevention of contrast-induced nephropathy: A randomized controlled trial of sodium bicarbonate and N-acetylcysteine.. The International journal of angiology : official publication of the International College of Angiology, Inc 18(4): 193-197

Sadat U, Walsh SR, Norden AG et al. (2011) Does oral N-acetylcysteine reduce contrast-induced renal injury in patients with peripheral arterial disease undergoing peripheral angiography? A randomized-controlled study.. Angiology 62(3): 225-230

Sar F, Saler T, Ecebay A et al. (2010) The efficacy of n-acetylcysteine in preventing contrast-induced nephropathy in type 2 diabetic patients without nephropathy.. Journal of nephrology 23(4): 478-482

Sharp, Alexander J., Patel, Nishith, Reeves, Barney C. et al. (2019) Pharmacological interventions for the prevention of contrast-induced acute kidney injury in high-risk adult patients undergoing coronary angiography: a systematic review and meta-analysis of randomised controlled trials. Open heart 6(1): e000864

Silva RG, Silva NG, Lucchesi F et al. (2010) Prevention of contrast-induced nephropathy by use of bicarbonate solution: preliminary results and literature review.. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia 32(3): 292-302

Sinert, R. and Doty, C. I. (2009) Update: prevention of contrast-induced nephropathy in the emergency department. Annals of Emergency Medicine 54(1): e1-e5

Su, Xiaole, Xie, Xinfang, Liu, Lijun et al. (2017) Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 69(1): 69-77

Subramaniam, Rathan M., Suarez-Cuervo, Catalina, Wilson, Renee F. et al. (2016) Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. Annals of internal medicine 164(6): 406-16

Subramaniam, Rathan M., Wilson, Renee F., Turban, Sharon et al. (2016) Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures. Agency for Healthcare Research and Quality (US). AHRQ Comparative Effectiveness Reviews, Report No.: 15(16)-EHC023-EF

Sun, Zikai, Fu, Qiang, Cao, Longxing et al. (2013) Intravenous N-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. PloS one 8(1): e55124

Tanaka A, Suzuki Y, Suzuki N et al. (2011) Does N-acetylcysteine reduce the incidence of contrast-induced nephropathy and clinical events in patients undergoing primary angioplasty for acute myocardial infarction?. Internal medicine (Tokyo, Japan) 50(7): 673-677

Thayssen, Per, Lassen, Jens Flensted, Jensen, Svend Eggert et al. (2014) Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. Circulation. Cardiovascular interventions 7(2): 216-24

Trivedi HS, Moore H, Nasr S et al. (2003) A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity.. Nephron. Clinical practice 93(1): c29

Valette, Xavier, Desmeulles, Isabelle, Savary, Benoit et al. (2017) Sodium Bicarbonate Versus Sodium Chloride for Preventing Contrast-Associated Acute Kidney Injury in Critically Ill Patients: A Randomized Controlled Trial. Critical care medicine 45(4): 637-644

Wang, Nelson, Qian, Pierre, Kumar, Shejil et al. (2016) The effect of N-acetylcysteine on the incidence of contrast-induced kidney injury: A systematic review and trial sequential analysis. International journal of cardiology 209: 319-27

Weisbord, Steven D., Gallagher, Martin, Kaufman, James et al. (2013) Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. Clinical journal of the American Society of Nephrology : CJASN 8(9): 1618-31

Wu, Mei-Yi, Hsiang, Hui-Fen, Wong, Chung-Shun et al. (2013) The effectiveness of N-Acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-

enhanced computed tomography: a meta-analysis of randomized controlled trials. International urology and nephrology 45(5): 1309-18

Xu, Renfan, Tao, Anyu, Bai, Yang et al. (2016) Effectiveness of N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association 5(9)

Yang, Kun, Liu, Wenxian, Ren, Wei et al. (2014) Different interventions in preventing contrast-induced nephropathy after percutaneous coronary intervention. International urology and nephrology 46(9): 1801-7

Yeganehkhah, Mohammad Reza, Iranirad, Leili, Dorri, Farshad et al. (2014) Comparison between three supportive treatments for prevention of contrast-induced nephropathy in high-risk patients undergoing coronary angiography. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 25(6): 1217-23

Zagler, Axel, Azadpour, Maziar, Mercado, Carlos et al. (2006) N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. American heart journal 151(1): 140-5

Zapata-Chica, Carlos Andres, Bello Marquez, Diana, Serna-Higuita, Lina Maria et al. (2015) Sodium bicarbonate versus isotonic saline solution to prevent contrast-induced nephropathy : a systematic review and meta-analysis. Colombia medica (Cali, Colombia) 46(3): 90-103

Zhang, Bin, Liang, Long, Chen, Wenbo et al. (2015) The efficacy of sodium bicarbonate in preventing contrast-induced nephropathy in patients with pre-existing renal insufficiency: a meta-analysis. BMJ open 5(3): e006989

Zhao, Shi-Jie, Zhong, Zhao-Shuang, Qi, Guo-Xian et al. (2016) The efficacy of N-acetylcysteine plus sodium bicarbonate in the prevention of contrast-induced nephropathy after cardiac catheterization and percutaneous coronary intervention: A meta-analysis of randomized controlled trials. International journal of cardiology 221: 251-9

Zoungas, S., Ninomiya, T., Huxley, R. et al. (2009) Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Annals of internal medicine 151(9): 631-638

Economic studies

Included studies

None

Excluded studies

Kooiman, de Vries, Van der Heyden, Sijpkens, van Dijkman, Wever et al. (2018) Randomized trial of one-hour sodium bicarbonate vs standard periprocedural saline hydration in chronic kidney disease patients undergoing cardiovascular contrast procedures. PloS one 13(2): e0189372.

Kooiman, Sijpkens, de Vries, Brulez, Hamming, van der Molen et al. (2014) A randomized comparison of 1-h sodium bicarbonate hydration versus standard peri-procedural saline

hydration in patients with chronic kidney disease undergoing intravenous contrast-enhanced computerized tomography. European Renal Association 29(5); 1029-36.

Kotlyar, Keogh, Thavapalachandran, Allada, Sharp, Dias et al. (2005) Prehydration alone is sufficient to prevent contrast-induced nephropathy after day-only angiography procedures--a randomised controlled trial. Heart, lung & circulation 14(4); 245-51.

Nijssen, Rennenberg, Nelemans, Essers, Janssen, Vermeeren et al. (2017) Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet 389: 1312-22

Appendix P – List of CI-AKI definitions

Table 34: List of CI-AKI definitions reported by included studies

CI-AKI definition
increase in sCr ≥25% or 44µmol/l
increase in sCr ≥25%
increase in sCr ≥44µmol/l
increase in sCr ≥44µmol/l or decrease of creatinine clearance of at least 25%
decrease in eGFR >25% between 1 to 4 days after contrast
increase in sCr or cystatin C concentration ≥25% or 44µmol/l
increase in sCr ≥44µmol/l or decrease in GFR ≥25% 48 hours after contrast
increase in sCr ≥25% or 44µmol/l or decrease in GFR of ≥5 ml/min
decrease in GFR of ≥5 ml/min
increase in sCr ≥25% or 26.5µmol/l
increase in sCr ≥ 26.5µmol/l

- *sCr: serum creatinine; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate*

Appendix Q – NMA models

Please refer to appendix R for the inconsistency models.

Fixed effects model for relative risk with input and output codes swapped

```
# Key data inputs: absID=9, outID = c(2, 16, 17, 14, 12, 15, 10, 13, 9, 6,
3, 7, 4, 8, 1, 11, 5)
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
  for (k in 1:na[i]) { # LOOP THROUGH ARMS 62- can do > 2 arms
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear
predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance
contribution
    + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
  resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution
for this trial
  }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment
effects
# reorder effects according to vector outID[]
for (k in 1:nt) {
  d3[k] <- d[outID[k]] - d[outID[1]]
  }
An <- 250 # estimate of absolute AKI prob with NaCl(0.9%)+NAC from Maioli
et al. (2008)
Ak <- 25
Ab <- An - Ak
A ~ dbeta(Ak, Ab)
for (k in 1:nt) {
  logit(T[k]) <- logit(A) + d3[k] + d[outID[1]] - d[absID]
  }
# RR for each treatment relative to reference option (use for caterpillar
plots)
RR[1] <- 1
for (k in 2:nt) {
  RR[k] <- T[k]/T[1]
  }
# pairwise ORs and RRs
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    OR[c,k] <- exp(d3[k] - d3[c])
    RRR[c,k] <- T[k]/T[c]
    }
  }
# rank treatments
for (k in 1:nt)  {
  rk[k]  <- rank(d3[],k)
  best[k]  <- equals(rk[k],1)    # Smallest is best (i.e. rank 1)
  for (h in 1:nt) {
```

```
    prob[h,k] <- equals(rk[k],h)
    }
  }
} # *** PROGRAM ENDS
```

Random effects model for relative risk with input and output codes swapped

```
# Key data inputs: absID=9, outID = c(2, 16, 17, 14, 12, 15, 10, 13, 9, 6,
3, 7, 4, 8, 1, 11, 5)
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0 # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
  for (k in 1:na[i]) { # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance
contribution
    + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
  resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution
for this trial
  for (k in 2:na[i]) { # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR
distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
(with multi-arm trial correction)
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-
arm RCTs
    taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with
multi-arm trial correction)
    sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm
trials
    }
  }
totresdev <- sum(resdev[]) #Total Residual Deviance
sd ~ dunif(0,5) # vague prior for between-trial SD. ALTERNATIVES BELOW
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
An <- 250 # estimate of absolute AKI prob with NaCl(0.9%)+NAC from Maioli
et al. (2008)
Ak <- 25
Ab <- An - Ak
A ~ dbeta(Ak, Ab)
for (k in 1:nt) {
  logit(T[k]) <- logit(A) + d3[k] + d[outID[1]] - d[absID]
  }
# RR for each treatment relative to reference option (use for caterpillar
plots)
RR[1] <- 1
for (k in 2:nt) {
  RR[k] <- T[k]/T[1]
  }
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
```

```
lor[c,k] <- (d[k]-d[c])
}
}
# pairwise ORs and RRs
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    OR[c,k] <- exp(d3[k] - d3[c])
    RRR[c,k] <- T[k]/T[c]
    }
  }
# rank treatments
for (k in 1:nt)  {
  rk[k]  <- rank(d3[],k)
  best[k]  <- equals(rk[k],1)    # Smallest is best (i.e. rank 1)
  for (h in 1:nt) {
    prob[h,k] <- equals(rk[k],h)
    }
  }
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment
effects
# reorder effects according to vector outID[]
for (k in 1:nt) {
  d3[k] <- d[outID[k]] - d[outID[1]]
  }
} # *** PROGRAM ENDS
```

Appendix R –NMA inconsistency checks

Introduction

The purpose of this analysis was to assess the consistency assumption in the network meta-analysis (NMA) model used to estimate the clinical and cost effectiveness of N-acetylcysteine (NAC) and/or fluids in preventing contrast induced acute kidney injury (CI-AKI) in at risk adults. Ocurrence of CI-AKI was the only outcome included in this analysis (see section 'NMA analyses and NMA model inconsistency checks' for more details about the inconsistency checks).

Methods

An important assumption made in NMA concerns the consistency of the direct and indirect evidence informing the treatment contrasts [1,2]. There should be no meaningful differences between these two sources of evidence.

To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an "inconsistency", or unrelated mean effects, model [1,2]. The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence [3].

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model [4]. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) [4].

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters, and thus penalizes model fit with model complexity [4]. Lower values are preferred and typically differences of 3-5 points are considered meaningful [4].

The posterior mean between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, was also used to compare models. When comparing consistency and inconsistency models, if the inconsistency model has the smallest heterogeneity, then this indicates potential inconsistency in the data.

We performed further checks for evidence of inconsistency through node-splitting [1-3,5]. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared.

Results

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 35).

Table 35: Model fit statistics

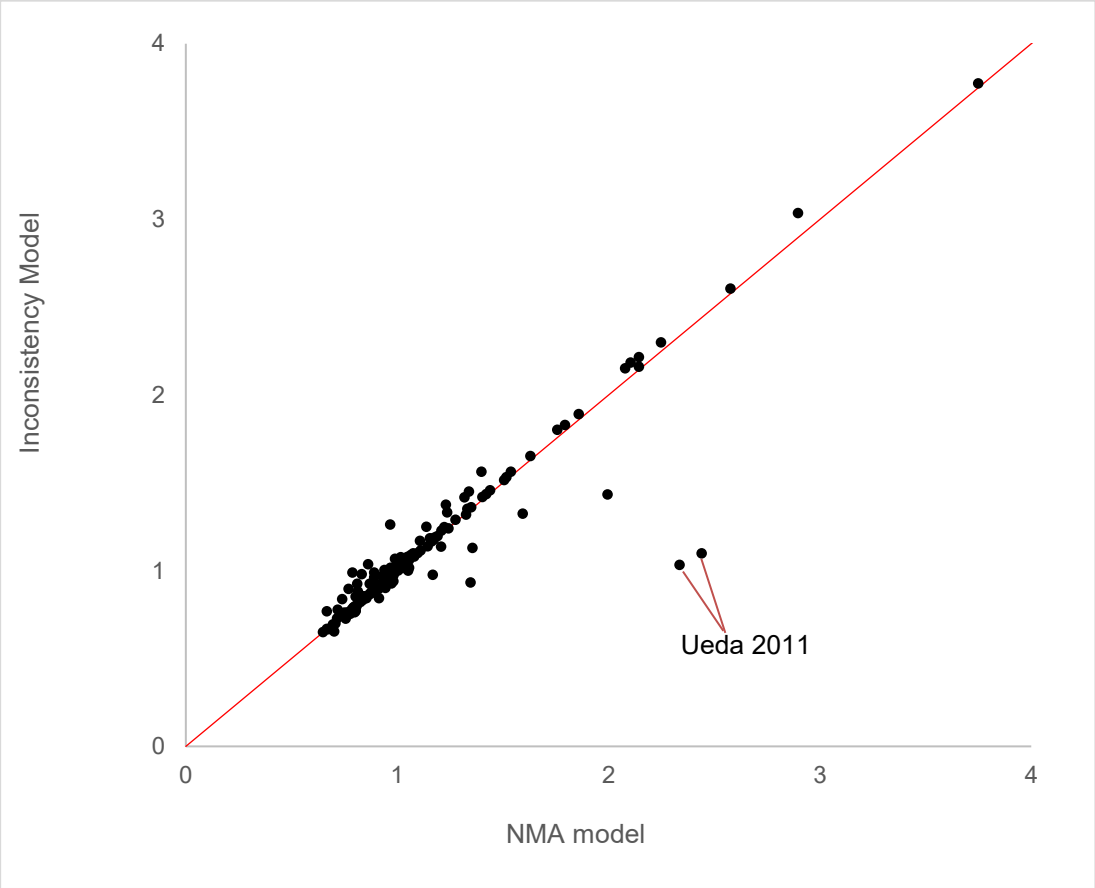
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	220.1	880.858
Random effects - consistency	0.47 (0.25, 0.71)	166.8	857.341
Random effects - inconsistency	0.46 (0.23, 0.71)	166.1	859.206

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 153 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 50,000 iterations on two chains. WinBUGS code for the inconsistency model is provided in Appendix R.1. WinBUGS code for inconsistency model used in this report

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 35). The area below the line of equality in Figure 34 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Ueda 2011 which included 2 of the treatments in the loop of evidence identified as potentially inconsistent in the node-splitting analysis (treatments: 3=sodium bicarbonate [IV] and 11=sodium chloride 0.9% [IV] + sodium bicarbonate [IV]). Ueda 2011 was better predicted by the inconsistency model. There were no errors in data extraction for Ueda 2011. Therefore, Ueda 2011 was removed from the data and the NMA models were run again (consistency and inconsistency models). Results were not too different compared to the models including all RCTs. Therefore, the committee decided to use the results with all RCTs when they discussed the evidence. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a significant decrease in the between-study heterogeneity (Table 35). See section of NMA analyses and NMA model inconsistency checks for a description of the inconsistency checks.

Figure 34: Deviance contributions for the random effects consistency and inconsistency models



Further checks for inconsistency using the node-splitting method (random effects model) found that there was evidence of inconsistency in the 1-3-11 loop, where 1 = sodium chloride 0.9% (IV), 3=sodium bicarbonate (IV), 11=sodium chloride 0.9% (IV) + sodium bicarbonate (IV). (Table 36, Figure 35-37). All RCTs involved in the 1-3-11 loop were scrutinised (no errors were found in data extraction) and there were no obvious differences in study characteristics that could account for the inconsistency. In addition to the relative effects estimated through NMA, we present direct (when available) and indirect estimates inTable 37. Where direct evidence is available on treatment comparisons, the direct and indirect estimates are reported based on results given by the node-splitting models. Otherwise, the indirect estimates are taken from the NMA model. All NMA estimates are reported based on the results from the random effects model that assumes consistency [6,7].

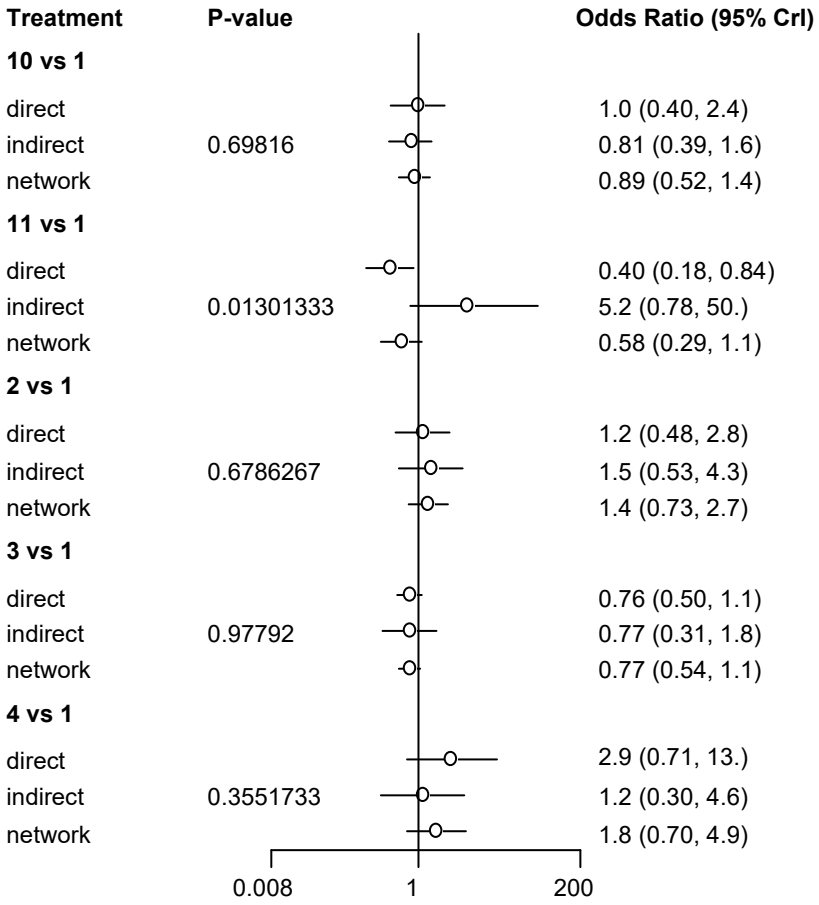
Table 36: Summary of node-splitting results

Node split model	Heterogeneity (SD)		Residual deviance[a]	p-value[b]	DIC
	median	95% CrI			
sodium chloride 0.9% (IV) vs NAC (oral) + sodium bicarbonate (IV)	0.52	(0.31, 0.78)	163.5	0.69	282.65
sodium chloride 0.9% (IV) vs	0.46	(0.24, 0.71)	163.05	0.01	278.03

Node split model	Heterogeneity (SD)		Residual deviance[a]	p-value[b]	DIC
	median	95% CrI			
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)					
sodium chloride 0.9% (IV) vs no (intravenous) hydration	0.47	(0.20, 0.73)	167.26	0.67	282.88
sodium chloride 0.9% (IV) vs sodium bicarbonate (IV)	0.54	(0.32, 0.80)	161.65	0.97	281.49
sodium chloride 0.9% (IV) vs sodium chloride 0.45% (IV)	0.48	(0.27, 0.73)	166.09	0.35	282.65
sodium chloride 0.9% (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	0.52	(0.29, 0.79)	162.35	0.32	280.54
NAC (oral) + sodium bicarbonate (IV) vs sodium bicarbonate (IV)	0.51	(0.28, 0.76)	163.72	0.67	281.71
NAC (oral) + sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	0.51	(0.28, 0.76)	164.43	0.45	282.86
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs NAC (IV) + sodium chloride 0.9% (IV)	0.51	(0.28, 0.76)	163.40	0.58	280.27
sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (IV)	0.44	(0.22, 0.68)	165.51	0.01	280.26
NAC (IV) + sodium chloride 0.9% (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	0.47	(0.25, 0.72)	165.26	0.72	280.93
no (intravenous) hydration vs sodium bicarbonate (IV)	0.49	(0.25, 0.74)	164.45	0.92	279.79
no (intravenous) hydration vs sodium chloride 0.45% (IV)	0.48	(0.26, 0.72)	166.12	0.36	282.55
sodium bicarbonate (IV) vs oral fluids	0.47	(0.25, 0.72)	167.35	0.49	284.91
sodium bicarbonate (IV) vs NAC (oral) + sodium chloride 0.9% (IV)	0.55	(0.33, 0.80)	160.78	0.49	279.75
NMA (no nodes split)	**0.48**	**(0.25, 0.72)**	**166.57**	**---**	**282.37**

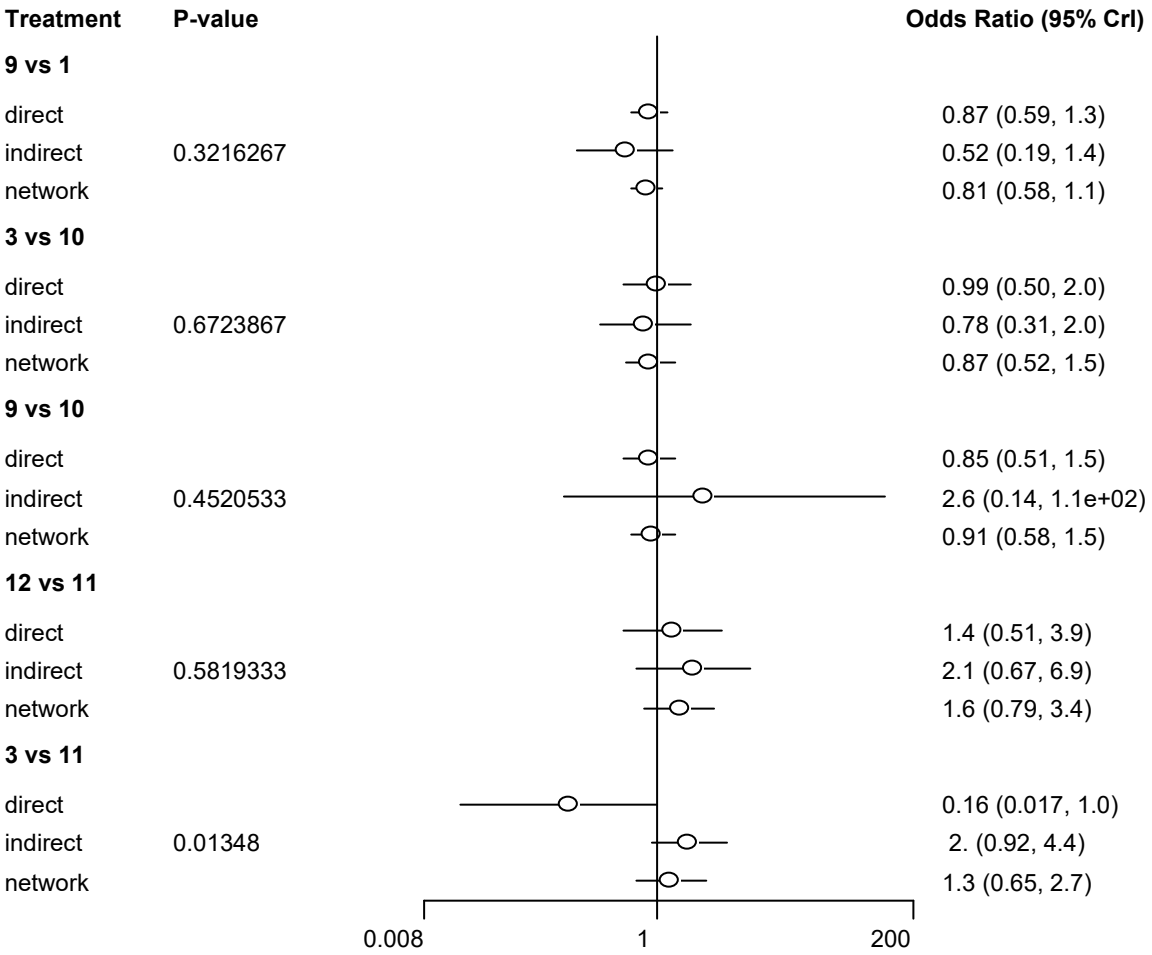
a) *Posterior mean residual deviance compared to 153 total data points*
b) *p-values <0.05 is indicative of evidence of inconsistency between the direct and indirect estimates*

Figure 35: Direct, indirect and network estimates of relative treatment effects based on node-splitting results (Part 1)



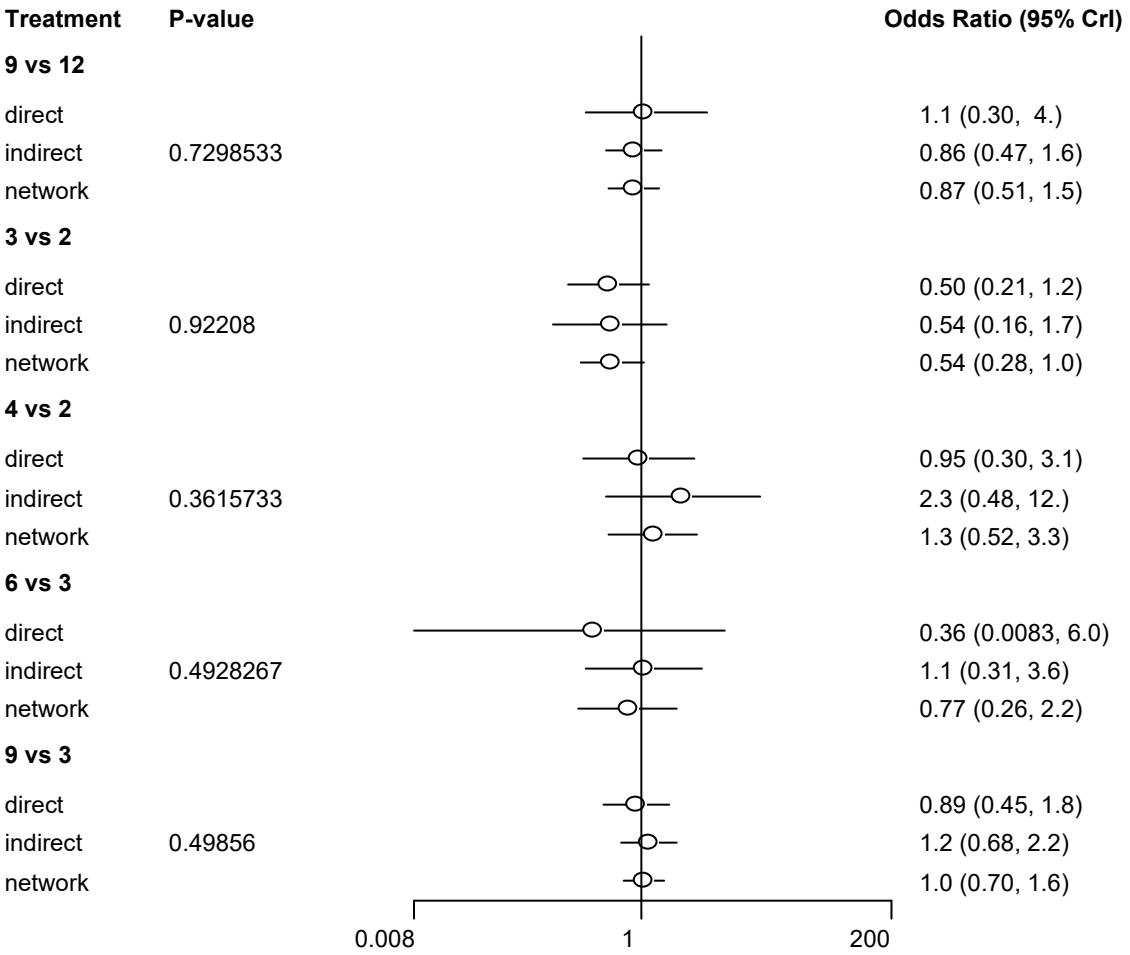
Treatment codes: 1=sodium chloride 0.9% (IV); 2=no (intravenous) hydration; 3=sodium bicarbonate (IV); 4=sodium chloride 0.45% (IV); 10=NAC (oral) + sodium bicarbonate (IV).

Figure 36: Direct, indirect and network estimates of relative treatment effects based on node-splitting results (Part 2)



Treatment codes: 1=sodium chloride 0.9% (IV) n; 3=sodium bicarbonate (IV); 9=NAC (oral) + sodium chloride 0.9% (IV); 10=NAC (oral) + sodium bicarbonate (IV); 11=sodium chloride 0.9% (IV) + sodium bicarbonate (IV); 12=NAC (IV) + sodium chloride 0.9% (IV).

Figure 37: Direct, indirect and network estimates of relative treatment effects based on node-splitting results (Part 3)



Treatment codes: 2=no (intravenous) hydration; 3=sodium bicarbonate (IV); 4=sodium chloride 0.45% (IV); 6=oral fluids; 9=NAC (oral) + sodium chloride 0.9% (IV); 12=NAC (IV) + sodium chloride 0.9% (IV).

Table 37: Direct, indirect and NMA estimates of all relative treatment effects[a]

Treatment 1	Treatment 2	Direct[b]			Indirect[c]			NMA[d]		
		median log(OR)	2.50%	97.50%	median log(OR)	2.50%	97.50%	median log(OR)	2.50%	97.50%
sodium chloride 0.9% (IV)	NAC (oral) + sodium bicarbonate (IV)	-0.00	-0.90	0.86	-0.21	-0.95	0.46	-0.11	-0.65	0.35
sodium chloride 0.9% (IV)	sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	-0.92	-1.72	-0.17	1.64	-0.25	3.91	-0.54	-1.23	0.10
sodium chloride 0.9% (IV)	no (intravenous) hydration	0.14	-0.74	1.01	0.42	-0.63	1.46	0.34	-0.31	0.97
sodium chloride 0.9% (IV)	sodium bicarbonate (IV)	-0.27	-0.68	0.10	-0.26	-1.17	0.59	-0.25	-0.60	0.06
sodium chloride 0.9% (IV)	sodium chloride 0.45% (IV)	1.07	-0.34	2.58	0.18	-1.20	1.52	0.59	-0.33	1.55
sodium chloride 0.9% (IV)	NAC (oral) + sodium chloride 0.9% (IV)	-0.13	-0.52	0.23	-0.65	-1.65	0.32	-0.21	-0.54	0.10
NAC (oral) + sodium bicarbonate (IV)	sodium bicarbonate (IV)	-0.00	-0.69	0.69	-0.24	-1.16	0.70	0.13	-0.39	0.65
NAC (oral) + sodium bicarbonate (IV)	NAC (oral) + sodium chloride 0.9% (IV)	-0.16	-0.67	0.38	0.96	-1.93	4.70	0.09	-0.39	0.54
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	NAC (IV) + sodium chloride 0.9% (IV)	0.32	-0.68	1.37	0.74	-0.40	1.93	0.47	-0.24	1.21
sodium chloride 0.9% (IV) + sodium bicarbonate (IV)	sodium bicarbonate (IV)	-1.81	-4.07	0.01	0.67	-0.08	1.47	-0.29	-1.01	0.42
NAC (IV) + sodium chloride 0.9% (IV)	NAC (oral) + sodium chloride 0.9% (IV)	0.08	-1.19	1.38	-0.15	-0.74	0.44	0.13	-0.40	0.67
no (intravenous) hydration	sodium bicarbonate (IV)	-0.69	-1.53	0.16	-0.62	-1.83	0.54	-0.60	-1.25	0.04
no (intravenous) hydration	sodium chloride 0.45% (IV)	-0.05	-1.21	1.11	0.84	-0.72	2.51	0.25	-0.65	1.2
sodium bicarbonate (IV)	oral fluids	-1.00	-4.79	1.79	0.06	-1.16	1.28	-0.25	-1.32	0.77

Treatment 1	Treatment 2	Direct[b]			Indirect[c]			NMA[d]		
		median log(OR)	2.50%	97.50%	median log(OR)	2.50%	97.50%	median log(OR)	2.50%	97.50%
sodium bicarbonate (IV)	NAC (oral) + sodium chloride 0.9% (IV)	-0.11	-0.80	0.57	0.18	-0.39	0.77	0.04	-0.35	0.46

a) Comparisons are presented in the form of Treatment 2 vs. Treatment 1
b) Direct estimates presented when available
c) Indirect estimates obtained from node-splitting models when direct evidence is available, otherwise equal to NMA estimates
d) Network meta-analysis (NMA) estimates obtained from random effects model, assuming consistency

Conclusion

There was evidence of inconsistency in the network. Data from Ueda 2011 and from the other studies involved in the 1-3-11 loop was scrutinised to ensure there were no errors that could account for this issue, but none were found. The committee expected that there would be inconsistency in the results because they were aware of intervention-level differences but these differences were accepted as part of the wide range of fluids regimens. Further checks for inconsistency using the node-splitting method (random effects model) found evidence of inconsistency between the direct and indirect estimates for two treatment comparisons: 1) sodium chloride 0.9% (IV) vs sodium chloride 0.9% (IV) + sodium bicarbonate (IV) and 2) sodium chloride 0.9% (IV) + sodium bicarbonate (IV) vs sodium bicarbonate (IV). Caution should be exercised when interpreting the results.

Appendix R.1. WinBUGS code for inconsistency model used in this report

```
# Binomial likelihood, logit link
# Random effects inconsistency model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0 # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
  for (k in 1:na[i]) { # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance
contribution
    + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
  resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution
for this trial
  for (k in 2:na[i]) { # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(d[t[i,1],t[i,k]],tau) # trial-specific LOR
distributions
    }
  }
totresdev <- sum(resdev[]) #Total Residual Deviance
for (c in 1:nt) {       d[c,c] <- 0 }
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  {
                  d[c,k] ~ dnorm(0,.0001)
                  d[k,c] <- -d[c,k]
                  }
  }
sd ~ dunif(0,5) # vague prior for between-trial SD. ALTERNATIVES BELOW
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

} # *** PROGRAM ENDS
```

References

1. Dias, S., Welton, N. J., Sutton, A. J., Caldwell, D. M., Lu, G., Ades, A. E., Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials, Medical Decision Making, 33, 641-656, 2013.

2. Dias, S., Welton, N. J., Sutton, A. J., Caldwell, D. M., Guobing, L., Ades, A. E., NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials, 2011, last updated April 2014, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/ 3. van Valkenhoef, G., Dias, S., Ades, A. E., Welton, N. J., Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis, Research Synthesis Methods, 7, 80-93, 2016

4. Spiegelhalter, D. J., Best, N. G., Carlin, B. P., van der Linde, A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

5. Dias, S., Welton, N. J., Caldwell, D. M., Ades, A. E., Checking consistency in mixed treatment comparison meta-analysis, Statistics in Medicine, 29, 932-944, 2010

6. Dias, S., Ades, A., Sutton, A., Welton, N., Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials, Medical Decision Making, 33, 607-617, 2013

7. Dias, S., Welton, N. J., Sutton, A. J., Ades, A. E., NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/