National Institute for Health and Care Excellence

Surveillance programme

Surveillance proposal consultation document

Acute kidney injury: prevention, detection and management NICE guideline CG169 – 4-year surveillance review

Background information

Guideline issue date: August 2013

Surveillance proposal for consultation

We will not update the guideline at this time.

We also propose to remove the following NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database:

- What is the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for adults with moderate to severe (stage 2 to 3) acute kidney injury not needing critical care?

Reason for the proposal

New evidence

We found 104 new studies in a search for randomised controlled trials (RCTs) and systematic reviews published between 01 January 2013 and 12 October 2016. We also considered 4 additional studies identified by members of the guideline committee who originally worked on this guideline.

From all sources, 108 studies were considered to be relevant to the guideline.

This included new evidence that is consistent with current recommendations:

- assessing the risk of acute kidney injury (AKI) in adults,
- preventing AKI in adults having iodinated contrast agents,
- monitoring and preventing deterioration in patients with or at high risk of AKI and,
- referring for renal replacement therapy.

We also identified new evidence in the following areas that was inconsistent with, or not covered by, current recommendations, but the evidence was not considered to impact on the guideline:

- remote ischemic conditioning to prevent contrast-induced AKI,
- pharmacological interventions to prevent contrast-induced AKI,
- severe AKI and short-term renal replacement therapy and,
- managing AKI in primary care.

We did not find any new evidence on identifying the causes of AKI, relieving urological obstruction, referral to nephrology and, information and support for patients and carers.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations. We asked topic experts whether this new evidence would affect current recommendations on preventing AKI in patients receiving iodinated contrast agents. Generally, the topic experts thought that an update was not needed.

No equalities issues were identified during the surveillance process.

Research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. See the research recommendations section for further information.

For this surveillance review we assessed 5 prioritised research recommendations, and proposed that 1 should be removed from the NICE version of the guideline and the NICE database.

Overall decision

After considering all the new evidence and views of topic experts, we decided not to update this guideline.

We also propose to remove 1 NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database.

Further information

See appendix A: summary of new evidence from surveillance below for further information.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Appendix A: summary of new evidence from surveillance

National Institute for Health and Care Excellence

4-year surveillance (2017) – Acute kidney injury: prevention, detection and management (2013) NICE guideline CG169

Appendix A: Summary of new evidence from surveillance

Assessing risk of acute kidney injury

169 – 01 Which risk assessment tools are the most accurate for predicting AKI in at risk adult patients?

Recommendations derived from this question

Identifying acute kidney injury in patients with acute illness

1.1.1 Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in adults with acute illness if any of the following are likely or present:

- chronic kidney disease (adults with an estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73 m^2 are at particular risk)
- heart failure
- liver disease
- diabetes
- history of acute kidney injury
- oliguria (urine output less than 0.5 ml/kg/hour)
- neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer
- hypovolaemia
- use of drugs with nephrotoxic potential (such as non-steroidal anti-inflammatory drugs [NSAIDs], aminoglycosides, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists [ARBs] and diuretics) within the past week, especially if hypovolaemic
- use of iodinated contrast agents within the past week
- symptoms or history of urological obstruction, or conditions that may lead to obstruction
- sepsis
- deteriorating early warning scores
- age 65 years or over.

Identifying acute kidney injury in patients with no obvious acute illness

1.1.3 Be aware that in adults, children and young people with chronic kidney disease and no obvious acute illness, a rise in serum creatinine may indicate acute kidney injury rather than a worsening of their chronic disease.

1.1.4 Ensure that acute kidney injury is considered when an adult, child or young person presents with an illness with no clear acute component and has any of the following:

- chronic kidney disease, especially stage 3B, 4 or 5, or urological disease
- new onset or significant worsening of urological symptoms
- symptoms suggesting complications of acute kidney injury
- symptoms or signs of a multi-system disease affecting the kidneys and other organ systems (for example, signs or symptoms of acute kidney injury, plus a purpuric rash).

Assessing risk factors in adults having iodinated contrast agents

1.1.5 Before offering iodinated contrast agents to adults for non-emergency imaging, investigate for chronic kidney disease by measuring eGFR or by checking an eGFR result obtained within the past 3 months.

1.1.6 Before offering iodinated contrast agents to adults for emergency or non-emergency imaging, assess their risk of acute kidney injury. Be aware that increased risk is associated with:

- chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m^2 are at particular risk)
- diabetes but only with chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m^2 are at particular risk)
- heart failure
- renal transplant
- age 75 years or over
- hypovolaemia
- increasing volume of contrast agent
- intra-arterial administration of contrast agent.
- Ensure that risk assessment does not delay emergency imaging.

1.1.7 Include the risks of developing acute kidney injury in the routine discussion of risks and benefits of the imaging procedure. Follow the recommendations on shared decision-making in Patient experience in adult NHS services (NICE clinical guidance 138).

Assessing risk factors in adults having surgery

1.1.8 Assess the risk of acute kidney injury in adults before surgery. Be aware that increased risk is associated with:

- emergency surgery, especially when the patient has sepsis or hypovolaemia
- intraperitoneal surgery
- chronic kidney disease (adults with an eGFR less than 60 ml/min/1.73 m^2 are at particular risk)
- diabetes
- heart failure
- age 65 years or over
- liver disease
- use of drugs with nephrotoxic potential in the perioperative period (in particular, NSAIDs after surgery).

Use the risk assessment to inform a clinical management plan.

1.1.9 Include the risks of developing acute kidney injury in the routine discussion of risks and benefits of surgery. Follow the recommendations on shared decision-making in Patient experience in adult NHS services (NICE clinical guidance 138).

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A multivariate logistic regression analysis[1] (n=1954), demonstrated that patients (with ST-segment elevation myocardial infarction (STEMI), unstable angina pectoris/non-STEMI (UAP/NSTEMI), and stable AP), undergoing emergency percutaneous coronary intervention were at risk of contrast induced-AKI (CI-AKI), regardless of their contrast media volume/estimated glomerular filtration rate ratio. An ejection fraction <40% and haemoglobin 10g/dL were also identified as predictors of CI-AKI.

A sub-study from an RCT[2] (sample size not reported) identified contrast volume, white blood cell count, left anterior descending infarct-related artery, age, anaemia creatinine clearance <60mL/min, and a history of congestive heart failure as predictors of CI-AKI after multivariable analysis.

Two studies investigated neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker:

A systematic review[3] (10 studies (type not reported), n=1310) reported urinary NGAL levels were significantly better at predicting CI-AKI than plasma/serum NGAL. However both plasma/serum and urinary NGAL levels were shown to be effective early indicators of CI-AKI.

A systematic review[4] (15 studies (type not reported), n=1478 septic patients) reported similar sensitivities for both plasma and urinary NGAL, however urinary NGAL was associated with greater specificity. Both urinary and plasma NGAL produced ROC curves of significantly good diagnostic accuracy. NGAL also demonstrated predictive value for renal replacement therapy (RRT) and mortality associated with AKI.

A post-hoc secondary analysis[5] (n=685 patients with AKI) analysed all-cause mortality and other outcomes by categories of serum ionised calcium (iCa). There was no significant difference in the number of days free from ICU or hospital, across different levels of iCa. A time-varying Cox regression survival model showed no difference in outcomes for levels of iCa>1mmol/L. Severe hypocalcaemia with iCa<1mmol/L independently predicted mortality in patients with AKI needing renal replacement therapy.

An RCT[6] (n = 70 patients) evaluated the use of serum cystatin C as a biomarker for predicting AKI. Patients had their levels of cystatin C measured at 6 time-points (T1-6) before, during and after cardiopulmonary bypass surgery. In predicting renal replacement therapy (RRT), serum cystatin C was higher after surgery. The end of surgery measurement (T4) produced the earliest significant predictor of AKI. Levels of cystatin C measured before and during surgery, showed limited diagnostic and predictive value.

A two period crossover RCT[7] (n=31 patients with type 2 diabetes) investigated the effects of 4g/day of long-chain n-3 polyunsaturated fatty acid (n-3 PUFA) supplementation on markers of kidney injury. Markers of kidney injury included: kidney-injury molecule-1, N-acetyl-β-d-glucosaminidase (NAG), NAGL, liver fatty acid-binding protein (LFABP), cystatin C, creatinine, β-2-microglobulin and, estimated glomerular filtration rate (eGFR). Compared with placebo, n-3 PUFA significantly reduced urine NGAL excretion. The authors concluded that there may be potential benefit of n-3 PUFA and reducing chronic kidney disease progression.

Topic expert feedback

Topic experts identified two studies:

A prospective observational study[8] (n=732 patients of which 213 patients developed AKI),

assessed the use of urinary angiotensinogen (uAGT) and other renal injury biomarkers as predictors of AKI. Multivariate analysis showed that there was a statistically significant prognostic association between AKI and urinary NGAL, uAGT, and urinary interleukin - 18.

A multicentre observational study[9] (n=522 patients critically ill and at risk of AKI), identified and validated biomarkers for AKI. There was a statistically significant association between Urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), and a diagnosis of AKI.

The topic experts felt that biomarker continued to be an area of interest. They highlighted NGAL and kidney injury molecule 1 (KIM-1) as novel biomarkers with NGAL- 'NephroCheck' the only FDA approved product. They felt that although the biomarkers were outside the original scope, current practice is already being influenced despite the lack of good quality evidence. The topic experts also commented on the lack of evidence the change of management after a biomarker for AKI is raised in an at-risk patient. The topic experts also commented on the need for health economic assessment of biomarkers.

Topic experts also identified an ongoing trial which has been described in the surveillance report. The study set in the UK, aims to identify risk factors and develop a risk score tool for AKI.

Impact statement

The new evidence is unlikely to impact on current recommendations: the new evidence investigated the use of NGAL as a biomarker, as well as identifying additional risk factors for CI-AKI specifically. The Guideline Committee did not originally consider individual risk factors, but validated risk tools. The recommendations reflected an absence of such tools, however, the risk factors identified during surveillance are captured within the current recommendation 1.1.6. The new evidence was consistent with current recommendations, however, the Guideline Committee did not consider the role of biomarkers in predicting AKI. The meta-analyses suggest that NGAL could be an effective early indicator of the development of AKI. However, no evidence of the impact of a raised NGAL on subsequent management was identified.

New evidence is unlikely to change guideline recommendations.

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169 – 02 Which risk assessment tools are the most accurate for predicting AKI in at risk paediatric patients?

Recommendations derived from this question

Identifying acute kidney injury in patients with acute illness

1.1.2 Investigate for acute kidney injury, by measuring serum creatinine and comparing with baseline, in children and young people with acute illness if any of the following are likely or present:

- chronic kidney disease
- heart failure
- liver disease
- history of acute kidney injury
- oliguria (urine output less than 0.5 ml/kg/hour)
- young age, neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a parent or carer
- hypovolaemia

- use of drugs with nephrotoxic potential (such as NSAIDs, aminoglycosides, ACE inhibitors, ARBs and diuretics) within the past week, especially if hypovolaemic
- symptoms or history of urological obstruction, or conditions that may lead to obstruction
- sepsis
- a deteriorating paediatric early warning score
- severe diarrhoea (children and young people with bloody diarrhoea are at particular risk)
- symptoms or signs of nephritis (such as oedema or haematuria)
- haematological malignancy
- hypotension

Identifying acute kidney injury in patients with no obvious acute illness

1.1.3 Be aware that in adults, children and young people with chronic kidney disease and no obvious acute illness, a rise in serum creatinine may indicate acute kidney injury rather than a worsening of their chronic disease.

1.1.4 Ensure that acute kidney injury is considered when an adult, child or young person presents with an illness with no clear acute component and has any of the following:

- chronic kidney disease, especially stage 3B, 4 or 5, or urological disease
- new onset or significant worsening of urological symptoms
- symptoms suggesting complications of acute kidney injury
- symptoms or signs of a multi-system disease affecting the kidneys and other organ systems (for example, signs or symptoms of acute kidney injury, plus a purpuric rash).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Preventing acute kidney injury

169 – 03 What is the predictive accuracy of paediatric early warning scores in detecting acutely ill children in hospital whose clinical condition is deteriorating or who are at risk of deterioration?

Recommendations derived from this question

Ongoing assessment of the condition of patients in hospital

1.2.1 Follow the recommendations in Acutely ill patients in hospital (NICE clinical guideline 50) on the use of track and trigger systems (early warning scores) to identify adults who are at risk of acute kidney injury because their clinical condition is deteriorating or is at risk of deteriorating

1.2.2 When adults are at risk of acute kidney injury, ensure that systems are in place to recognise and respond to oliguria (urine output less than 0.5 ml/kg/hour) if the track and trigger system (early warning score) does not monitor urine output.

1.2.3 Consider using a paediatric early warning score to identify children and young people admitted to hospital who are at risk of acute kidney injury because their clinical condition is deteriorating or is at risk of deteriorating.

- Record physiological observations at admission and then according to local protocols for given paediatric early warning scores.

- Increase the frequency of observations if abnormal physiology is detected.

1.2.4 If using a paediatric early warning score, use one with multiple-parameter or aggregate weighted scoring systems that allow a graded response and:

- define the parameters to be measured and the frequency of observations
- include a clear and explicit statement of the parameters, cut-off points or scores that should trigger a response.

1.2.5 If using a paediatric early warning score, use one with multiple-parameter or aggregate weighted scoring systems that measure:

- heart rate
- respiratory rate
- systolic blood pressure
- level of consciousness
- oxygen saturation
- temperature
- capillary refill time.

1.2.6 When children and young people are at risk of acute kidney injury because of risk factors in recommendation 1.1.2:

- measure urine output
- record weight twice daily to determine fluid balance
- measure urea, creatinine and electrolytes
- think about measuring lactate, blood glucose and blood gases.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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169 – 04 What is the comparative clinical and cost effectiveness of NAC and/or intravenous fluids in preventing CI-AKI in at risk patients?

Recommendations derived from this question

Preventing acute kidney injury in adults having iodinated contrast agents

1.2.7 Offer intravenous volume expansion to adults having iodinated contrast agents if:

- they are at increased risk of contrast-induced acute kidney injury because of risk factors in recommendation 1.1.6, or
- they have an acute illness.

Offer either isotonic sodium bicarbonate or 0.9% sodium chloride.

1.2.8 Consider temporarily stopping ACE inhibitors and ARBs in adults having iodinated contrast agents if they have chronic kidney disease with an eGFR less than 40 ml/min/1.73 m^2.

1.2.9 Discuss care with a nephrology team before offering iodinated contrast agent to adults with contraindications to intravenous fluids if:

- they are at increased risk of contrast-induced acute kidney injury, or

- they have an acute illness, or
- they are on renal replacement therapy.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

N-acetylcysteine

Five studies were identified, which studied the effects of n-acetylcysteine (NAC) infusion in patients at risk of AKI, after contrast administration:

A pre-specified subgroup analysis from an RCT[10] (n=1395 diabetic patients undergoing coronary and peripheral vascular angiography) evaluated the use of acetylcysteine vs placebo, in preventing CI-AKI. The incidence of CI-AKI was similar in both groups. No difference was observed between both groups in the combined endpoint of death or need for dialysis at 30 days.

A meta-analysis[11] (13 RCTs, n=1420 patients undergoing open-heart surgery) assessed whether NAC had preventative effects on CI-AKI. The incidence of post-operative AKI was reduced compared to those in the placebo group, however this effect was not seen in the high-risk cohort. No statistical difference was seen in the length of hospital stay or change in serum creatinine, between both groups.

An RCT[12] (n=70 chronic kidney disease patient, stage 3 or 4, undergoing coronary artery bypass graft surgery, with or without cardiopulmonary bypass) investigated the renal protective-effects of NAC compared with saline. The incidence of AKI was significantly reduced in NAC group compared with the saline group. Non-use of NAC was identified as an independent predictor of AKI. These effects were observed in both patient cohorts that were or were not treated with a cardiopulmonary bypass.

A meta-analysis[13] (10 RCTs, n=1916 patients) assessed the use of intravenous NAC for the prevention of CI-AKI. The comparison was not reported. There was a reduced incidence of CI-AKI in those who received NAC, however, this was not a statistically significant result. The authors concluded that more robust research was needed.

A meta-analysis[14] (6 RCTs, n=496 patients undergoing coronary angiography) investigated the role of NAC in preventing CI-AKI. A statistically significant reduction in the incidence of CI-AKI, was observed in the NAC group compared to the control. Those who received NAC, were also given hydration. No significant difference was seen in the number of people requiring RRT, between both groups.

Sodium bicarbonate

Eight studies were identified, which studied the effects of sodium bicarbonate infusion in patients at risk of AKI, after contrast administration:

An individual patient meta-analysis[15] (n=877 from 3 RCTs) investigated the effects of urine alkalisation and prevention of AKI. Patients were originally randomised to receive either 24 hours of intravenous infusion of sodium bicarbonate or sodium chloride. Sodium bicarbonate increased serum bicarbonate and urine pH. However, there was no statistically significant difference in the post-operative increase of serum creatinine, between the two groups. After study adjustment, in elective coronary artery surgery bypass surgery, a statistically significant benefit of sodium bicarbonate was seen in terms of renal replacement therapy and the development of AKI.

A systematic review and meta-anlysis[16] (16 RCTs, n=3537 patients undergoing coronary angiography and/or percutaneous coronary intervention) investigated the use of sodium bicarbonate vs sodium chloride to prevent CI-AKI. Hydration with sodium bicarbonate showed statistically significant benefit in preventing CI-AKI. However, no significant difference was observed in mortality, the number of people requiring dialysis and, length of hospital stay.

A multicentre RCT[17] (n=350 patients undergoing open heart surgery) investigated the use of sodium bicarbonate vs sodium

chloride to preventing AKI after cardiac surgery. The study was stopped early due to lack of efficacy and possible harm. There was significant increase of the incidence of CI-AKI, in those that received sodium bicarbonate. Hospital mortality was increased in those receiving sodium bicarbonate compared to those in the sodium chloride group.

A meta-analysis[18] (5 RCTs, n=1092 patients) compared sodium bicarbonate to sodium chloride in preventing AKI associated with surgery. No statistical difference was seen between both groups, in incidence of AKI, in-hospital mortality, need for renal replacement therapy and, length of ICU stay.

An open-label multicentre RCT[19] (n=138 patients chronic kidney disease) compared sodium bicarbonate to no hydration, in preventing CI-AKI. There was no difference in the incidence of CI-AKI, between groups. None of the patients diagnosed with CI-AKI went on to need RRT, in either group.

A multicentre RCT[20] (N=427 patients scheduled to undergo elective cardiac surgery) investigated the use of sodium bicarbonate vs sodium chloride to preventing AKI after surgery. There was no difference in incidence of AKI, mortality, ICU or hospital length of stay, between both groups.

A systematic review and meta-analysis[21] (5 RCTs, n=1079 patients undergoing cardiac surgery) investigated the use of sodium bicarbonate in preventing AKI, compared with placebo. Sodium bicarbonate did not significantly reduce: the risk of AKI, length of hospital stay, RRT use and, mortality, compared to placebo. Sodium bicarbonate was associated with a significant increase in the risk of ICU length of stay and, adverse events.

An interim analysis from a multicentre RCT[22] (n=120 patients) assessed the use of sodium bicarbonate perioperatively, compared to saline. Sodium bicarbonate was associated with a statistically significant increase risk of AKI. The study was stopped early on the advice of the data safety monitoring board.

A systematic review and meta-analysis[23] (22 RCTs, n=5686 patients) compared sodium bicarbonate to isotonic saline solution, in preventing CI-AKI. There was no significant difference observed between both groups, in the need for RRT or mortality.

A meta-analysis[24] (20 RCTs, n=4280) assessed the use of sodium bicarbonate in preventing CI-AKI. Sodium bicarbonate given in combination with hydration, significantly reduced the incidence of CI-AKI. The incidence of CI-AKI was significantly reduced in those treated with sodium bicarbonate. The composition of the contrast agent also influenced the efficacy of the sodium bicarbonate. Sodium bicarbonate given with NAC, significantly reduced the incidence of CI-AKI, compared with sodium bicarbonate alone. No statistically significant difference in mortality or need for RRT was observed in those treated with sodium bicarbonate.

Hydroxyethyl starch

Five studies were identified, which studied the effects of hydroxyethyl starch (HES), after contrast administration:

A post-hoc analysis[25] (n=798 patients with severe sepsis) compared the effects of hydroxyethyl starch (HES) with Ringer's solution on mortality with AKI. There was a significant increase in the incidence of severe AKI in those given HES, 5 days after randomisation. Significantly, more patients in the HES group received RRT within the first 5 days, and the time to initiation of RRT was also shorter compared with the Ringer's group.

A systematic review and meta-analysis[26] (42 studies, n=11,399 patients) assessed HES vs alternate fluid therapy for the prevention or treatment of effective intravascular volume depletion. A statistically significant increase in need for RRT in the HES group was observed, compared to those receiving alternate fluid therapy. An increase in the incidence of kidney failure was also observed in the HES group. Using the RIFLE-F (failure) criteria, a significant increase in the risk of AKI associated with those receiving HES, was reported.

A systematic review and meta-analysis[27] (10 RCTs, n=4624 patients with sepsis) assessed the role of fluid resuscitation with HES compared with crystalloids. A statistically significant increase in the incidence of AKI, and need for RRT was found in patients who received resuscitation with HES. Intensive care unit mortality, and 28 day mortality showed no difference between the two groups. However, HES was associated with higher rates of mortality at 90 days, than the crystalloid group.

A meta-analysis[28] (15 RCTs, n=4409 surgical patients) investigated the effects of HES on postoperative RRT. HES was associated with a statistically significant increase in the number of

patients requiring RRT, compared with non-HES infusions. Subgroup analysis showed no difference in this effect when comparing surgical to non-surgical patients.

A systematic review and meta-analysis[29] (38 RCTs, n=10880 patients (7 trials, n=590 were later retracted due to scientific misconduct)) assessed the role of HES in AKI, amongst many comparators including: crystalloids, albumin, or gelatine. There was a statistically significant increase in mortality, in those treated with HES compared with control. A statistically significant increase in renal failure and, need for RRT was also observed in the HES group.

Oral hydration

Three studies were identified, which studied the effects oral hydration, after contrast administration:

A systematic review and meta-analysis[30] (6 RCTs, n=513 patients undergoing elective procedures with normal to moderately reduced kidney function) assessed the use of oral hydration for the prevention of CI-AKI. Patients received either an oral hydration regimen or intravenous (IV) fluid regimen. There was no statistically significant increased risk of CI-AKI in the oral regimen group. The authors concluded that an oral fluid regimen as a possible alternative which could be offered to patients in an outpatient setting for the prevention of AKI.

A systematic review and meta-analysis[31] (6 RCTs, n=513 patients) compared the efficacy of oral vs IV volume expansion in preventing CI-AKI. No difference was observed in the incidence of CI-AKI, between groups.

An RCT[32] (n =328 patients scheduled for major elective open abdominal surgery) investigated whether preoperative intravenous hydration with normal saline could prevent postoperative AKI. There was no difference in the incidence of AKI between the saline group and control. There was also no significant difference in adverse events between both groups.

An RCT[33] (n=396 patients aged >18 years undergoing cardiac catheterisation with an eGFR of 60mL/min/1.73m^2) investigated the use of haemodynamic-guided fluid administration for the prevention of CI-AKI. Patients were randomised to receive left ventricular end-diastolic pressure-guided volume expansion or the control group (standard fluid administration protocol). The frequency of CI-AKI was reduced in those who received the intervention compared to the control.

A multicentre RCT[34] (n=474 critically ill patients) investigated whether daily IV amino acid supplementation would preserve GFR during critical illness. Patients were randomised to receive either standard care or to IV amino acid therapy. Amino acid therapy significantly improved eGFR, however, no difference in the duration of renal dysfunction was observed between the groups. There was a statistically significant increase in urinary output observed in the IV amino acid group.

A systematic review and network meta-analysis[35] (150 RCTs, n=31,631 patients) assessed 12 treatment strategies for preventing CI-AKI:NAC, statin, statin with NAC, sodium bicarbonate, sodium bicarbonate with NAC aminophylline, fenoldopam, iloprost, alprostadil, prostaglandin E1, vitamin C, vitamin E, alpha—lipoic acid, atrial natrieutic peptide, B-type natriuretic peptide, and carperitide. All of the interventions were investigated in combination with hydration. High-dose statins with or without NAC, produced statistically significant reductions in the incidence of CI-AKI, in comparison to hydration alone.

A systematic review and meta-analysis[36] (9 RCTs, n=626 patients) assessed the use of mannitol in preventing AKI. There was a statistically significant reduction in the incidence of AKI and need for RRT compared with expansion of intravascular volume alone. However, no difference was observed in high risk patients for either outcome.

A cluster-randomised, double crossover RCT[37] (n=2278 patients admitted to the ICU requiring crystalloid fluid therapy) investigated the use of buffered crystalloid solution in managing AKI, compared with saline solution. No statistically significant difference was observed between the two groups in the incidence of AKI within 90 days and, need for RRT. There was statistically significant reduction in mortality in those who were given mannitol.

1 study was identified that considered fenoldopam, however this drug is not available in the UK so not discussed further.

1 study was identified that considered carperitide, however this drug is not available in the UK so not discussed further.

Topic expert feedback

A topic expert highlighted one RCT[33] which was identified in the 4 year surveillance review

search and is described above. The topic expert confirmed AKI occurs after cardiac catheterisation and coronary procedures in a moderate number of patients in the UK.

Impact statement

The new evidence identified is not likely to impact on current recommendations. The new evidence is inconclusive regarding the benefit of NAC in preventing CI-AKI. NAC was associated with non-significant reductions in the incidence of CI-AKI, when compared with placebo or other interventions in both RCTs and meta-analyses. However, 1 meta-analysis showed a statistically significant reduction in the incidence of CI-AKI, in patients given NAC combined with hydration. Currently, recommendation 1.2.7 does not recommend NAC for the prevention of CI-AKI. Oral hydration with sodium bicarbonate and Evidence assessing the use of NAC was reviewed by the Guideline Committee in 2013, however the evidence was of very low quality. Sodium bicarbonate is currently recommended for use in recommendation 1.2.7, however, new evidence is inconclusive as to the actual effectiveness of sodium bicarbonate in preventing CI-AKI specifically. This evidence could impact current recommendations. The use of mannitol was also seen to be effective, however only one studied was identified. It is unknown at this point whether this would have an impact on current recommendations and further research is needed. Currently, CG169 does not contain any recommendations on the use of HES in preventing CI-AKI, therefore the new evidence is unlikely to have an impact.

New evidence is unlikely to change guideline recommendations

169 – 05 What is the clinical and cost effectiveness of methods for preventing inappropriate use of nephrotoxic drugs in hospital inpatients?

Recommendations derived from this question

Monitoring and preventing deterioration in patients with or at high risk of acute kidney injury

1.2.10 Consider electronic clinical decision support systems (CDSS) to support clinical decision-making and prescribing, but ensure they do not replace clinical judgement.

1.2.11 When acquiring any new CDSS or systems for electronic prescribing, ensure that any systems considered:

- can interact with laboratory systems
- can recommend drug dosing and frequency
- can store and update data on patient history and characteristics, including age, weight and renal replacement therapy
- can include alerts that are mandatory for the healthcare professional to acknowledge and review.

1.2.12 Seek advice from a pharmacist about optimising medicines and drug dosing in adults, children and young people with or at risk of acute kidney injury.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A cluster RCT[38] (n= 1278 patients with AKI) in an in-patient and out-patient setting of a university hospital, evaluated the use of real-time alerting on appropriate prescribing in kidney disease. Physicians were randomised to receive clinical decision support for renal dose adjustments or to continue their usual workflow. The authors reported that a greater proportion of prescriptions were appropriately adjusted in those randomised to the intervention compared to the control. They reported that prospective alerts had a greater impact than look-back

alerts. The study concluded that clinical decision support improved medicine prescribing.

An RCT[39] (n= 2393 patients aged over 18 years or older, with stage 1 or greater KIDGO (Kidney Disease Improving Outcomes) AKI) randomised patients to receive an acute kidney injury alert (a text-based alert sent to the covering provider and unit pharmacist indicating new AKI) or usual care. The authors reported that an electronic alert system for AKI did not improve patient outcomes.

Topic expert feedback

A topic expert highlighted one RCT[39] which was identified in the 4 year surveillance review search and is described above.

A topic expert identified an observational study[40] (n=15,550 patients) which observed the effects of installing a real-time AKI e-alert system, in an NHS hospital. The study reported an increase in mortality in relation to advancing stages of AKI.

Topic experts felt that although e-alerts were outside the original scope, current practice is already being influenced despite the lack of good quality evidence. Topic experts advised that primary care should also be issued with e-alerts, and practical referral guidance. This would ensure consistency and equality across both primary and secondary care.

Impact statement

The new evidence affirms of the current recommendations and therefore will have no impact on them. The new evidence suggests that some electronic alert systems are better than others in reducing inappropriate prescribing in patients with AKI. This is in line with recommendations 1.2.10-1.2.12. Topic experts commented on the need for such interventions to be made available in primary care, however, no evidence was found to suggest that there would be additional benefit in this care setting.

New evidence is unlikely to change guideline recommendations.

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169 – 06 What is the clinical and cost effectiveness of stopping compared to continuing chronic ACEI and/or ARB therapy to prevent AKI due to diarrhoea and vomiting, or sepsis?

Recommendations derived from this question

Monitoring and preventing deterioration in patients with or at high risk of acute kidney injury

1.2.13 Consider temporarily stopping ACE inhibitors and ARBs in adults, children and young people with diarrhoea, vomiting or sepsis until their clinical condition has improved and stabilised.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A multivariate Cox model[41] (n=1463) evaluated the role of ACEI in slowing the progression of AKI. The authors reported a significant reduction in mortality at 90 days and a reduction in RRT-free days, associated with ACEI use. However, these effects were diminished after adjustment for time-dependent covariates. The authors concluded that further evaluation of ACEI use in AKI was needed.

A meta-analysis[42] (16 RCTs, n= 113,386), evaluated the safety and efficacy of ARBs in patients over 65 years. The study found a marginal increased risk of both all-cause mortality and, AKI in those receiving ARBs compared to placebo. The authors concluded

that ARBs should be used with caution in older patients when clinically indicated.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The results of the new evidence are unlikely to impact on current recommendations. The new evidence investigated the continuation of ACEI therapy and its effect on outcomes. Currently recommendation 1.2.13 states that such therapy may be stopped temporarily, within the context of adverse events such as diarrhoea and vomiting (D & V) and sepsis. There are no recommendations currently dealing with the use of ACEI in the absence of adverse symptoms, whilst the patient is experiencing AKI. The new evidence does not definitively establish the basis for recommending the continuation or discontinuation of ACEIs in the absence of D&V or sepsis, therefore further research is needed. The evidence in relation to the use of ARBs in older patients is consistent with recommendation 1.2.13, and the rest of the guideline.

New evidence is unlikely to change guideline recommendations.

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169 – 07 What is the clinical and cost effectiveness of stopping compared to continuing chronic ACEI and/or ARB therapy in patients with CKD to prevent AKI due to surgery or iodinated contrast? (No recommendations made in the guideline)

Surveillance decision

This review question should not be updated.

4-year surveillance summary

An RCT[43] (n=208 patients with moderate renal insufficiency) randomised patients to hold ACEI/ARB >24 hrs before cardiac catheterisation or continue ACEI/ARB. All patients were taking an ACEI (72.1%) or ARB (27.9%) prior to randomisation. There was a non-significant increase in the incidence of AKI, in the group which continued on ACE/ARB therapy compared to those who had their therapy held. There was a significant reduction in post-surgery rises in creatinine in those whose ACEI/ARB was held.

A systematic review and meta-analysis[44] (1 RCT, 23 cohort studies; n=102,675 patients) investigated the risk of postoperative AKI in patients who received renin-angiotensin system (RAS) inhibitors prior to surgery. The authors concluded that there was an association between preoperative RAS inhibitor use and lower incidence of AKI after surgery. Within individual studies there was no statistically significant effect on mortality observed.

A multivariate Cox model[41] (n=1463) evaluated the role of ACEI in slowing the progression of AKI. The authors reported a significant reduction in mortality at 90 days and a reduction in RRT-free days, associated with ACEI use. However, these effects were diminished after adjustment for time-dependent covariates. The authors concluded that further evaluation of ACEI use in AKI was needed.

Topic expert feedback

The topic experts noted that the guideline did not discuss the timing of stopping and restarting ACEI/ARBs in patients at risk of AKI/after recovery from an episode of AKI. Topic experts noted that CG169 looked at a very limited number of specific drugs. They noted that there is uncertainty and variation in dosing of various drugs and threshold for stopping some renally excreted drugs in AKI. The dosing of renally excreted antibiotics in AKI, dosing of drugs in the context of RRT, and the use of low molecular weight heparins, were also raised as areas of interest.

Impact statement

There are currently no recommendations on the stopping/continuing ACEI/ARBs in CG169 due to the absence of evidence; the new evidence identified no significant difference in mortality or concluded that further research is needed to demonstrate a benefit in either stopping or continuing ACEI/ARBs in patients at risk of AKI The new evidence is insufficient to trigger an update of this question and the addition of new recommendations.

New evidence is unlikely to change guideline recommendations.

Detecting of acute kidney injury

169 – 08 What is the clinical evidence that RIFLE (pRIFLE) or AKIN or KDIGO are useful in detecting and staging AKI and predicting patient outcomes (mortality and RRT)?

Recommendations derived from this question

Detecting of acute kidney injury

1.3.1 Detect acute kidney injury, in line with the (p)RIFLE[3], AKIN[4] or KDIGO[5] definitions, by using any of the following criteria:

- a rise in serum creatinine of 26 micromol/litre or greater within 48 hours
- a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days
- a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people
- a 25% or greater fall in eGFR in children and young people within the past 7 days.

1.3.2 Monitor serum creatinine regularly[6] in all adults, children and young people with or at risk of acute kidney injury.

Identifying the cause(s) of acute kidney injury

1.4.1 Identify the cause(s) of acute kidney injury and record the details in the patient's notes.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Identifying the cause(s) of acute kidney injury

169 – 09 What is the sensitivity and specificity of urine dipstick compared to urine microscopy and/or biopsy in the detection of proteinuria and haematuria as indicators of glomerulonephritis in AKI patients?

Recommendations derived from this question

Urinalysis

1.4.2 Perform urine dipstick testing for blood, protein, leucocytes, nitrites and glucose in all patients as soon as acute kidney injury is suspected or detected. Document the results and ensure that appropriate action is taken when results are abnormal.

1.4.3 Think about a diagnosis of acute nephritis and referral to the nephrology team when an adult, child or young person with no obvious cause of acute kidney injury has urine dipstick results showing haematuria and proteinuria, without urinary tract infection or trauma due to catheterisation.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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169 – 10 Which patients should have US for the diagnosis of the cause of AKI?

Recommendations derived from this question

Ultrasound

1.4.4 Do not routinely offer ultrasound of the urinary tract when the cause of the acute kidney injury has been identified.

1.4.5 When pyonephrosis (infected and obstructed kidney[s]) is suspected in adults, children and young people with acute kidney injury, offer immediate ultrasound of the urinary tract (to be performed within 6 hours of assessment).

1.4.6 When adults, children and young people have no identified cause of their acute kidney injury or are at risk of urinary tract obstruction, offer urgent ultrasound of the urinary tract (to be performed within 24 hours of assessment).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Managing acute kidney injury

169 – 11 In adults and children with AKI and upper tract urological obstruction, what is the clinical and cost effectiveness of early compared to delayed

relief of obstruction by nephrostomy or stenting on mortality, severity of AKI, need for RRT and length of hospital stay?

Recommendations derived from this question

Relieving urological obstruction

1.5.1 Refer all adults, children and young people with upper tract urological obstruction to a urologist. Refer immediately when one or more of the following is present:

- pyonephrosis
- an obstructed solitary kidney
- bilateral upper urinary tract obstruction
- complications of acute kidney injury caused by urological obstruction.

1.5.2 When nephrostomy or stenting is used to treat upper tract urological obstruction in adults, children and young people with acute kidney injury, undertake as soon as possible and within 12 hours of diagnosis.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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169 – 12 In adults and children with AKI, what is the clinical and cost effectiveness of loop diuretics compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and hearing loss?

Recommendations derived from this question

Pharmacological management

1.5.3 Do not routinely offer loop diuretics to treat acute kidney injury.

1.5.4 Consider loop diuretics for treating fluid overload or oedema while:

- an adult, child or young person is awaiting renal replacement therapy, or
- renal function is recovering in an adult, child or young person not receiving renal replacement therapy.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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169 – 13 In adults and children with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, need for RRT,

length of RRT, dialysis independence, length of hospital stay and cardiac arrhythmias?

Recommendations derived from this question

Pharmacological management

1.5.5 Do not offer low-dose dopamine to treat acute kidney injury.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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169 – 14 In patients with AKI, what is the clinical and cost effectiveness of initiating early RRT compared to delayed RRT on mortality, renal recovery, duration of RRT, length of critical care stay and HRQoL?

Recommendations derived from this question

Referring for renal replacement therapy

1.5.6 Discuss any potential indications for renal replacement therapy with a nephrologist, paediatric nephrologist and/or critical care specialist immediately to ensure that the therapy is started as soon as needed.

1.5.7 When an adult, child or young person has significant comorbidities, discuss with them and/or their parent or carer and within the multidisciplinary team whether renal replacement therapy would offer benefit. Follow the recommendations on shared decision-making in Patient experience in adult NHS services (NICE clinical guidance 138).

1.5.8 Refer adults, children and young people immediately for renal replacement therapy if any of the following are not responding to medical management:

- hyperkalaemia
- metabolic acidosis
- symptoms or complications of uraemia (for example, pericarditis or encephalopathy)
- fluid overload
- pulmonary oedema.

1.5.9 Base the decision to start renal replacement therapy on the condition of the adult, child or young person as a whole and not on an isolated urea, creatinine or potassium value.

1.5.10 When there are indications for renal replacement therapy, the nephrologist and/or critical care specialist should discuss the treatment with the adult, child or young person and/or their parent or carer as soon as possible and before starting treatment. Follow the recommendations on shared decision-making in Patient experience in adult NHS services (NICE clinical guidance 138).

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A multicentre RCT[45] (n=620 patients with severe acute kidney injury, Kidney Disease Improving Global Outcomes (KDIGO) stage 3) was comparing the efficacy of early and delayed initiation of renal replacement therapy. There was no significant difference in the 60-day mortality rate in both the early and delayed strategy groups.

An open-label RCT[46] (n=208 patients with community acquired AKI) compared earlier start and usual start dialysis. Earlier start dialysis (intervention group) was initiated when serum urea nitrogen and/or creatinine levels increased to 70 and 7 mg/dL, respectively, whereas the usual-start dialysis patients (control group) received dialysis when judged appropriate by a nephrologist. There was a non-significant decrease in serum urea nitrogen and creatinine in the intervention group.

A systematic review and meta-analysis[47] (6 RCTs, n=1257) investigated the timing of initiation of RRT for AKI. Early RRT did not significantly reduce the risk of mortality or RRT dependency, compared to late RRT.

An RCT[48] (n=231 critically patients with AKI KDIGO stage 2) compared the effect of early initiation RRT versus delayed initiation RRT. Early initiation was defined as RRT started within 8 hours of diagnosis of KDIGO stage 2; delayed initiation was defined as RRT started within 12 hours of KDIGO stage 3 or no initiation. Early initiation of RRT significantly reduced 90-day mortality/ compared with delayed initiation. Duration of RRT and length of hospital stay were significantly shorter in the early group than in the delayed group. There was no significant difference in the continued need for RRT across both groups.

Topic expert feedback

The topic experts identified two RCTs[45],[48] which were identified in the 4 year surveillance review search and are described above.

Topic experts raised issues with the variation in practice of RRT, timing, choice and use of anticoagulation in AKI. They noted these areas not currently covered by the guideline.

Impact statement

The new evidence is unlikely to impact on current recommendations. Currently the guideline does not make mention of the timing of RRT, however, the new evidence is inconclusive as to whether there is benefit or equivalence in early or delayed RRT. There is more evidence to suggest that there is no difference in effect on mortality when RRT is offered early. The guideline committee may choose to make a recommendation which addresses this; stating that both practices appear to be equivalent in effectiveness. This is difficult to attain from the abstracts and would require the critique of a guideline committee, if deemed necessary.

New evidence is unlikely to change guideline recommendations.

169 – 15 In patients with or suspected of having AKI, what is the clinical and cost effectiveness of early compared to delayed referral to a nephrologist?

Recommendations derived from this question

Referring to nephrology

1.5.11 Refer adults, children and young people with acute kidney injury to a nephrologist, paediatric nephrologist or critical care specialist immediately if they meet criteria for renal replacement therapy in recommendation 1.5.8.

1.5.12 Do not refer adults, children or young people to a nephrologist or paediatric nephrologist when there is a clear cause for acute kidney injury and the condition is responding promptly to medical management, unless they have a renal transplant.

1.5.13 Consider discussing management with a nephrologist or paediatric nephrologist when an adult, child or young person with severe illness might benefit from treatment, but there is uncertainty as to whether they are nearing the end of their life.

1.5.14 Refer adults, children and young people in intensive care to a nephrology team when there is uncertainty about the cause of acute kidney injury or when specialist management of kidney injury might be needed.

1.5.15 Discuss the management of acute kidney injury with a nephrologist or paediatric nephrologist as soon as possible and within 24 hours of detection when one or more of the following is present:

- a possible diagnosis that may need specialist treatment (for example, vasculitis, glomerulonephritis, tubulointerstitial nephritis or myeloma)
- acute kidney injury with no clear cause
- inadequate response to treatment
- complications associated with acute kidney injury
- stage 3 acute kidney injury (according to (p)RIFLE, AKIN or KDIGO criteria)
- a renal transplant
- chronic kidney disease stage 4 or 5.

1.5.17 Consider referral to a paediatric nephrologist for children and young people who have recovered from an episode of acute kidney injury but have hypertension, impaired renal function or 1+ or greater proteinuria on dipstick testing of an early morning urine sample.

Surveillance decision

No new information was identified at any surveillance review

This review question should not be updated.

Information and support for patients and carers

169 – 16 What information and support do patients with acute kidney injury and their carers require?

Recommendations derived from this question

1.6.1 Discuss immediate treatment options, monitoring, prognosis and support options as soon as possible with people with acute kidney injury and/or, if appropriate, their parent or carer. Follow the recommendations on patient views and preferences and shared decision-making in Patient experience in adult NHS services (NICE clinical guidance 138).

1.6.2 Give information about long-term treatment options, monitoring, self-management and support to people who have had acute kidney injury (and/or their parent or carer, if appropriate) in collaboration with a multidisciplinary team appropriate to the person's individual needs.

1.6.3 Give information about future care to people needing renal replacement therapy after discharge following acute kidney injury. This should include information about the frequency and length of dialysis sessions and the preparation needed (such as having a fistula or peritoneal catheter).

1.6.4 Discuss the risk of developing acute kidney injury, particularly the risk associated with conditions leading to dehydration (for example, diarrhoea and vomiting) and drugs with nephrotoxic potential (including over-the-counter NSAIDs), with people who are at risk of acute kidney injury, particularly those who have:

- chronic kidney disease with an eGFR less than 60 ml/min/1.73 m^2
- neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer.

Involve parents and carers in the discussion if appropriate.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NQ – 01 What is the clinical and cost effectiveness of using remote ischemic conditioning to prevent contrast-induced AKI?

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This question should not be added.

4-year surveillance summary

A meta-analysis[49] (10 RCTs, n=1389 patients) investigated the effect of remote ischemic conditioning (RIC) on CI-AKI, after PCI or coronary artery angiography. There was statistically significant reduction in the incidence of CI-AKI, in those treated with RIC compared with controls. There was no significant reduction in 30-day mortality in the RIC group compared with control. RIC received before the surgery significantly reduced the incidence of CI-AKI, compared with after surgery.

A meta-analysis[50] (37 RCTs, n=8168 patients), assessed the effects of RIC on AKI, compared to a control group. A statistically significant reduction in incidence of AKI, as defined by the authors, in the RIC group compared to controls. This effect was diminished when applying RIFLE (Risk, Injury, Failure, Loss, End Stage), AKIN (Acute Kidney Injury Network), or KDIGO (Kidney Disease Improving Global Outcome) diagnostic criteria for AKI was applied. Subgroup analysis showed that a reduction in the incidence of AKI was only statistically significant in patients who received RIC and underwent PCI compared to cardiac surgery. No significant difference was observed in the need for RRT, between both groups.

A systematic review and meta-analysis[51] (20 RCTs, n= 3357 patients undergoing CABG and 1501 patients undergoing PCI) evaluated the use of RIC in preventing AKI. There was a statistically significant reduction in the incidence of AKI after PCI, in those who received RIC compared to the control group. This effect was not observed in patients who underwent CABG. No statistically significant reduction in the need for RRT or hospital mortality, was observed between the RIC and control group.

A meta-analysis[52] (9 RCTs, n= not reported) assessed the effects of RIC on AKI associated with PCI. A statistically significant reduction in the incidence of AKI was observed in those who received RIC, compared with controls. RIPoC produced a statistically significant reduction in the incidence of AKI postoperatively, compared with the control group, as did RIPC.

Pre-conditioning

A systematic review and meta-analysis[53] (30 RCTs, n= not reported) assessed the role of remote ischemic pre-conditioning (RIPC) in preventing AKI. There was a significant reduction in the incidence of AKI (including CI-AKI) in those who underwent RIPC, compared with the control. No difference was observed in AKI associated with ischemia/reperfusion. There was no observable difference in the incidences of stage 1-3 AKI, need for RRT, 30-day mortality or length of hospital day, between both groups.

A meta-analysis[54] (10 RCTs, n=924 patients undergoing cardiac or vascular surgery) assessed the role of RIPC in preventing AKI. There was statistically significant reduction in the incidence of AKI, in the RIPC group compared with control. No significant difference was observed between the two groups in the need for RRT, mortality, length of hospital stay and, length of ICU stay.

A meta-analysis[55] (11 RCTs, n=1713 patients with stable coronary artery disease) evaluated the perioperative effects of RIPC. There was a statistically significant reduction in the incidence of CI-AKI, in those treated with RIPC compared to the control group.

A meta-analysis[56] (27 RCTs, n= 5652 patients undergoing cardiac or vascular surgery) assessed the use of RIPC in cardiac surgery. There was a statistically significant reduction in the incidence of CI-AKI and, length of hospital stay, in those treated with RIPC compared to the control group. No statistically significant difference was observed in all-cause mortality, between both groups.

An RCT[57] (n=128 high risk patients having had cardiac surgery within the last 30 days) investigated the post-operative effects of RIPC compared to a sham procedure. No statistically significant difference was observed in the incidence of AKI, between both groups.

An RCT[58] (n=125 patients with suspected ST-elevation myocardial infarction) assessed the post-operative effects of RIPC compared to a sham procedure. There was statistically significant reduction in the incidence of CI-AKI, in those who received the RIPC intervention compared with the sham group.

A meta-analysis[59] (13 RCTs, n=1334 patients undergoing cardiac or vascular surgery) evaluated the use of RIPC in preventing AKI. There was statistically significant reduction in the incidence of CI-AKI, in those who received the RIPC intervention compared with the control group. No statistically significant difference was observed in the need for RRT;

hospital mortality; length of hospital stay and, length of ICU stay, between both groups.

A systematic review and meta-analysis[60] (19 studies, n= 5100 patients undergoing on-pump cardiac surgery) investigate the effect of RIPC on post-operative AKI. A statistically significant reduction in the incidence of AKI, was seen in those who received RIPC compared to controls. However, no statistically significant difference was seen in the need for RRT and, hospital mortality, between both groups.

A multicentre RCT[61] (n=240 patients undergoing cardiac surgery), investigated the effect of RIPC on AKI, compared to a sham procedure. There was a statistically significant reduction in the risk of AKI, in those that received RIPC compared to the sham group. A statistically significant reduction in length of ICU stay, was also seen in this group. No significant difference in mortality was observed between the two groups.

Post-conditioning

An RCT[62] (n=225 patients with non-ST-segment elevation myocardial infarction, undergoing elective coronary angiography) evaluated the effectiveness of remote ischemic post-conditioning (RIPoC) using repeated intermittent balloon inflations, in preventing AKI after PCI. There was a statically significant reduction in the incidence of AKI, in the RIPoC group compared with sham controls. A significant reduction in 30-day mortality was also observed in the RIPoC group compared with sham controls.

Topic expert feedback

A topic expert highlighted one RCT[61] which was identified in the 4 year surveillance review search and is described above. However, the topic expert commented that there was only a small proportion of AKI patients requiring cardiac surgery in the UK.

Impact statement

The new evidence is unlikely to impact on the guidelines. Currently, CG169 only recommends volume expansion as a method of preventing CI-AKI (recommendation 1.2.7). New evidence has demonstrated the use of remote ischemic conditioning, specifically prior to surgery, as reducing the incidence of CI-AKI. However, this is likely to be a desirable secondary outcome of the surgical procedure. NICE is developing a guideline on perioperative care and it was considered that RIC could be covered in the new guideline. Covering this area in a new guideline on perioperative care would allow RIC to be considered for its effects on wider clinical outcomes. Therefore, a new question on remote ischemic conditioning will not be added.

New evidence is unlikely to impact on the guideline.

NQ – 02 In patients with severe AKI what type of short-term RRT should be considered?

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This question should not be added.

4-year surveillance summary

A systematic review[80] (24 studies, including 4 RCTs, n=1556) evaluated use of peritoneal dialysis in AKI. The overall methodological quality of the studies included was reported as low. There was no difference in mortality when the studies were pooled. There was significant heterogeneity amongst the trials. There was no evidence to suggest a significant difference in mortality between peritoneal dialysis and extracorporeal blood purification in AKI.

A systematic review and meta-analysis[81] (4 RCTs, n=470) compared the use of high-volume hemofiltration (HVHF) with standard-volume hemofiltration (SVHF) for the treatment of septic AKI. There was no significant difference in 28-day mortality between both types of hemofiltration. Hypophosphatemia and hypokalaemia were more commonly observed in the HVHF, though this was not consistently reported across the studies.

A systematic review and meta-analysis[82] (6 RCTs, n= 3185 patients with AKI in ICU) investigated the intensity of continuous renal replacement therapy for AKI. Intensive continuous renal replacement therapy (CRRT), prescribed 35mL/kg/h was compared with less intensive CRRT, prescribed <35 mL/kg/h. No significant difference between intensive versus less intensive CRRT was observed in: mortality risk, RRT dependency, no of ICU/hospital days. One study reported an increased the risk of hypophosphatemia with intensive RRT. After subgroup analysis by the severity of illness and aetiology of AKI, intensive CRRT seemed to reduce the risk of mortality in patients with surgery induced AKI.

An RCT[83] (n=1464) investigated the long-term outcomes of differing RRT modalities in patients who had had AKI. Quality of life was not different between those who received higher intensity of RRT and those who received lower intensity. There was no significant difference in the number of survivor at 90 days between both groups, or the number of people requiring future RRT.

A multicentre RCT[84] (n=1124 critically ill patients with severe AKI, requiring initiation of RRT) compared intensive and less intensive RRT strategies. Intensive strategies were defined as: haemodialysis or sustained low-efficiency dialysis six times per week or continuous venovenous hemodiafiltration at 35ml/kg per hour; less intensive strategies were defined as: haemodialysis or sustained low-efficiency dialysis three times per week or continuous venovenous hemodiafiltration at 20ml/kg per hour. Unadjusted models suggest an association between intensive RRT strategies and a greater reduction in urine output i.e. a worsening of AKI in critically ill patients.

An open-label RCT[85] (n=212 septic patients receiving CRRT for management of AKI) investigated the role of continuous venovenous hemodiafiltration (CVVHDF) dose on inflammatory cytokine removal, known to exacerbate sepsis-induced AKI. Conventional (40mL/kg/h) and high (80mL/kg/h) doses of CVVHDF were compared. Initiation criteria was not controlled. There was no statistically significant difference in 28 –day mortality between the two dosage groups. However, high dose CVVHDF significantly reduced interleukin 6 (IL-6), IL-8, IL-1b and IL-10 level. CRRT did not appear to impact on clinical outcomes despite inflammatory cytokine removal.

An RCT[86] (n=252 critically ill patients with AKI), investigated the effect of intermittent haemodialysis (IHD) and continuous veno-venous hemofiltration (CVVH) on mortality and renal outcomes. No statistically significant differences were observed in the number of days on RRT, or ICU/hospital stay or survival at 14 days after RRT. Both strategies were concluded to be equivalent options when deciding the appropriate type of RRT in patients with severe AKI.

A systematic review and meta-analysis[87] (23 studies including 7 RCTs, n=472 patients) compared the rate of dialysis in those who received intermittent RRT or CRRT. No statistically significant difference in the rate of dialysis dependence was observed between the two groups. A meta-analysis of observational studies reported a statistically significant increase in the rate of dialysis dependency in those who received intermittent RRT.

Topic expert feedback

A topic expert noted that CRRT is currently is widely used in ICUs in the UK.

Impact statement

The specificity of RRT including its type, dose and frequency in patients with AKI, is not discussed in CG169. The new evidence suggests that the different modalities of RRT

are equivalent in their performance when assessing outcomes such as mortality or hospital stay. The evidence suggests there may be benefit in some options in averting adverse effects such as hypokalaemia, hypophosphatemia. A new RRT guideline is currently in development, however the use of RRT as short term management of AKI will not be covered. Due to the inconclusiveness of the evidence, the addition of this question will be reviewed again at future surveillance reviews.

New evidence is unlikely to impact on the guideline.

NQ – 03 In patients having surgery, which pharmacological interventions are clinically and cost effective in reducing the risk of developing AKI?

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This question should not be added.

4-year surveillance summary

A multicentre, multinational, RCT[63] (n = 6905 patients undergoing non-cardiac surgery) investigated whether aspirin compared with placebo and, clonidine compared with placebo altered the risk of perioperative acute kidney injury. Aspirin did not change the risk of AKI, but increased the risk of bleeding, which is associated with increased risk of subsequent AKI. Clonidine increased the risk of hypotension, which similarly is associated with an increased risk of subsequent AKI. Neither aspirin nor clonidine affected the risk of AKI.

An RCT[64] (n= 213 patients with poor renal function undergoing elective percutaneous coronary intervention (PCI)), investigated whether continuous intravenous nicorandil infusion compared with saline, prevented CI-AKI. Nicorandil treatment saw a statistical reduction in the overall average increase in serum creatinine and cystatin C following PCI, compared with the saline group. The incidence of CI-AKI was significantly reduced in those who received nicorandil. Univariate regression analysis showed that nicorandil use as a statistically significant predictor of CI-AKI development.

An RCT[65] (n=60 paediatric patients aged 6-72 months, undergoing cardiac angiography) investigated the effects of dexmedetomidine on early stage renal function. A statistically significant reduction in the incidence of CI-AKI was seen in the group which received dexmedetomidine, compared to the control group.

A systematic review and meta-analysis[66] (10 RCTs, n= 1600 patients undergoing cardiac surgery) assessed the use of volatile anaesthetics for preventing AKI. A statistically significant reduction in the incidence of CI-AKI in those that received volatile anaesthetics, compared with placebo. There was also a significant reduction in the incidence of prolonged stay in ICU; and, hospitalisation, in those treated with volatile anaesthetics compared with placebo.

An RCT[67] (n= 409 patients with septic shock) investigated the effects of vasopressin on AKI, compared with norepinephrine. A statistically significant reduction in number of patients who developed AKI in those who were treated with norepinephrine compared with vasopressin. There was a significant reduction in the need for RRT in those treated with vasopressin, compared with norepinephrine. No significant

difference was seen in mortality between both groups.

A meta-analysis[68] (8 studies (study type not reported), n=11542 patients) investigated the effect of time between coronary angiography to cardiac surgery, and AKI. There was a statistically significant increase in the incidence of AKI, in those that had an interval of 1 day or less between both surgeries. A statistically significant reduction in the incidence was see in those that had an interval of 3 days or more between both surgeries.

A review of systematic reviews[69] (7 systematic reviews, n=not reported) investigated the use of pharmaceutical interventions in preventing AKI. There were no statistically significant differences in outcomes (incidence of AKI; need for RR; and, mortality), in those treated with: NAC; dopamine; and, fenoldopam.

A systematic review and meta-analysis[70] (4 studies including 2 RCTs, n=543 patients) investigated the use nebivolol for preventing CI-AKI. A statistically significant difference was seen in those given nebivolol, compared with placebo. This effect was diminished when the meta-analysis was restricted to just the RCTs.

A systematic review of RCTs and quasi-randomised trial[71] (2 RCTs, n= 97 patients), compared the any dose or form of thyroid hormone therapy alone or in combination with other agents compared with placebo or supplemental treatment (such as furosemide, dopamine, or atrial natriuretic peptide) in adults patients with AKI. The two studies were not meta-analysed due to differences in the cause of AKI. The authors reported an increase in all-cause mortality associated with thyroid therapy compared with placebo in one study, however none were reported in the other. No incidence of progression to end-stage kidney disease; and no significant difference in the need for RRT associated with thyroid therapy compared with placebo in either study. The authors concluded that thyroid hormone interventions should be avoided in patients with AKI, due to worse outcomes. They highlighted the need for further research.

Anti-inflammatory

A post-hoc analysis from an RCT[72] (n=4465 patients) analysed the use of dexamethasone in preventing postoperative AKI. A statistically significant reduction in severe AKI, which was defined as a need for RRT, in those that received dexamethasone compared to the placebo group. Further subgroup analysis, demonstrated these effects were exaggerated in patients with an eGFR <15 mL/min/1.73m^2.

A meta-analysis[73] (14 RCTs, n=931 patients undergoing cardiac surgery), investigated the use of anti-inflammatory strategies in preventing AKI. No statistically significant difference was seen in the incidence of AKI, in those given steroids or miniaturised extracorporeal circuits, compared with placebo. A statistically significant reduction in the incidence of AKI was seen in those treated with leukocyte filters.

Anti-oxidants

A multicentre RCT[74] (n=300 patients undergoing coronary angiography) assessed the use of short-term alpha-tocopherol (vitamin E) supplementation in preventing CI-AKI. There was a statistically significant difference in the incidence of CI-AKI in those that were given vitamin E compared with placebo. Multivariate analysis showed that's baseline Mehran score and vitamin E were statistically significant predictors of AKI.

A systematic review and meta-analysis[75] (9 RCTs, n=1536 patients), assessed the role of ascorbic acid (vitamin C) in preventing CI-AKI. There was a statistically significant reduction in the risk of developing CI-AKI, in those receiving ascorbic acid compared with placebo.

A meta-analysis[76] (11 RCTs, n=1848 patients undergoing cardiac surgery), assessed the use of antioxidants (vitamin E and vitamin C), in preventing CI-AKI. A statistically significant reduction in the risk of CI-AKI was seen in those that were given anti-oxidation supplementation, compared with placebo.

Erythropoietin

A systematic review and meta-analysis[77] (6 RCTs, n=473 patients undergoing cardiac surgery) assessed the use of erythropoietin (EPO) in preventing AKI. There was no statistically significant difference in the incidence of AKI, in those that received EPO prior to surgery compared with placebo. Subgroup analysis showed a statistically significant reduction in the incidence of AKI, when EPO was given prior to anaesthesia compared with placebo. This effect was also seen in low risk patients.

A meta-analysis[78] (5 RCTs, n=423 patients undergoing cardiac surgery), investigated the use of EPO in preventing AKI. No statistically significant difference in the incidence of AKI,

was seen in those treated with EPO compared with placebo. Subgroup analysis showed a statistically significant reduction in: the incidence of AKI; length of hospital stay; and, length of ICU stay in low-risk patients treated with EPO.

A systematic review and meta-analysis[79] (10 RCTs, n= 2759 patients who are either critically or receiving perioperative treatment) investigated the use of EPO in the prevention of AKI. No statistically significant difference: in the incidence of AKI; need for RRT; and, mortality in those given EPO compared with placebo.

1 study was identified that considered fenoldopam, however this drug is not available in the UK so not discussed further.

Statins

A meta-analysis[88] (8 RCTs, n=4734 patients undergoing coronary angiography), evaluated the effects of statins at different doses on CI-AKI, compared to placebo. Those who received statins, were dosed over a short-term period. The duration of treatment, dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the incidence of CI-AKI was seen at both high-level and low-level doses of statins, compared with the placebo group. However meta-regression analysis, showed no significant reduction in the risk of CI-AKI between both groups, or specifically in diabetic patients.

A systematic review and meta-analysis[89] (13 RCTs, n=304 patients), investigated the effects of statins given perioperatively on CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. Both the statin and control groups were treated with Intravenous fluid hydration, in all the included studies. There was a statistically significant reduction in the incidence of CI-AKI in those given statins perioperatively, compared to the control group.

A meta-analysis[90] (15 RCTs, n=not reported) investigated the effects of statins given prior to cardiac surgery, on CI-AKI. There was a statistically significant reduction in the risk of CI-AKI in those treated with statins, compared to placebo. The duration of treatment, dosage level or choice of statin was not reported in the abstract. There was a non-significant reduction in the need for RRT, observed in this group. A significant reduction in the risk of CI-AKI was also observed in patients receiving high dose statins compared with low dose statins. Subgroup analysis showed a significant reduction in the incidence of CI-AKI, in patients with: diabetes; heart failure; chronic kidney disease; and, patients who received more than 140mL of contrast agent.

A meta-analysis[91] (8 RCTs, n= 4984 patients undergoing coronary catheterisation) investigated the use of statins prior to surgery for preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. There was a significant reduction in the incidence of CI-AKI in the group of patients treated with statins, compared to the control group. A statistically significant reduction in the risk of CI-AKI was also seen in the statin group. Subgroup analysis by renal function (GFR < or > 60mL/min) did not diminish the difference in incidence of CI-AKI. No association was see between the incidence of CI-AKI and statin-type; and NAC or hydration.

A meta-analysis[92] (13 RCTs, n= 5825 patients undergoing coronary angiography) assessed the use of high-dose statins compared with low-dose statin or placebo, in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the incidence of CI-AKI, was seen in the high-dose group, compared with low-dose statin or placebo. Subgroup analysis showed that this effect was maintained, independent of: presence of chronic kidney disease; presence of acute coronary syndrome; age; composition of contrast agent; and, administration of NAC.

A meta-analysis[93] (21 RCTs, n=7746 patients undergoing coronary angiography or PCI) assessed the short-term use of statins in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. There was a statistically significant reduction in the risk of CI-AKI, in those treated with high dose statins compared with both placebo and low-dose stains. Subgroup analysis showed that this effect was maintained, independent of: prior risk of CI-AKI; definition of CI-AKI; patients' naïve to statins; type of statin; composition of contrast; use of NAC or hydration; and East Asian demographic.

A meta-analysis[94] (17 studies (type not reported), n= 18684 patients undergoing cardiac surgery) investigated the use of statins in preventing AKI. The duration of treatment,

dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the incidence of CI-AKI was observed in those given statins, compared with controls. A statistically significant reduction in mortality was also observed, in this group.

A meta-analysis[95] (9 RCTs, n=5212 patients undergoing coronary angiography or PCI) assessed the use of statins in preventing CI-AKI. A statistically significant reduction in the risk of CI-AKI was seen in those treated with statins, compared to the control group. Subgroup analysis showed a statistically significant reduction of the risk of CI-AKI, in those with acute coronary syndromes in the statin group.

A systematic review and meta-analysis[96] (24 studies including 5 RCTs, n=989173 patients undergoing major surgery) assessed the preoperative use of statins in preventing AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. There was no statistically significant reduction in the risk of post-operative AKI, in those that received statins prior to surgery. A statistically significant reduction in risk of need for RRT, was seen in those given statins prior to surgery.

A systematic review and meta-analysis[97] (9 RCTs, n=5143 patients) assessed the use of statins in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the risk of CI-AKI was observed in those that received statins, compared with placebo. This reduction was also seen independent of baseline renal impairment; and, treatment with NAC.

A systematic review and network meta-analysis[35] (150 RCTs, n=31,631 patients) assessed 12 treatment strategies for preventing CI-AKI:NAC, statin, statin with NAC, sodium bicarbonate, sodium bicarbonate with NAC aminophylline, fenoldopam, iloprost, alprostadil, prostaglandin E1, vitamin C, vitamin E, alpha—lipoic acid, atrial natrieutic peptide, B-type natriuretic peptide, and carperitide. All of the interventions were investigated in combination with hydration. High-dose statins with or without NAC, produced statistically significant reductions in the incidence of CI-AKI, in comparison to hydration alone.

A meta-analysis[98] (19 RCTs, n=7161 patients undergoing coronary angiography) investigated the preoperative use of statins in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the incidence of CI-AKI was observed in those given statins preoperatively, compared with controls. Patients with stage 3 chronic kidney disease did not make up a significant proportion of the sample. The reduction in the incidence of CI-AKI, was non-significant in these patients.

A meta-analysis[99] (12 RCTs, n=5564 patients undergoing coronary angiography) investigated the preoperative use of statins in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. There was a statistically significant reduction in the incidence of CI-AKI, in those treated with high-dose statins in comparison to low-dose statins or placebo. Subgroup analysis showed that this effect was not seen in diabetic patients or those with baseline renal impairment.

A meta-analysis[100] (17 studies, n=6323 patients) assessed the use of statins in preventing CI-AKI. There was a significant reduction in the incidence of CI-AKI in the group of patients treated with statins prior to surgery. Statin use was associated with a statistically significant reduction in the need for RRT; and, all-cause mortality at 30 days.

Simvastatin

An RCT[101] (n=6245 patients with chronic kidney disease and not on dialysis) investigated the role of simvastatin (20mg daily) combined with ezetimibe, in slowing the progression of kidney disease. There was no statistically significant reduction in the incidence of end-stage kidney disease, after 4.8 year follow-up, compared with placebo. No significant difference in mortality was seen between both groups.

Atorvastatin

An RCT102 (n=615 patients undergoing cardiac surgery), investigated the effects of atorvastatin (40 & 80 mg daily) in preventing AKI. The trial was stopped early due to an increased incidence of AKI in patients with chronic kidney disease. No significant difference was observed in the incidence of AKI between the atorvastatin and placebo group. There was a significant increase in the incidence of AKI, in patients who were naïve to statin treatment before the trial, compared with placebo. No significant difference was

observed in the incidence of AKI, in patients who were receiving statins prior to the trial, compared with placebo.

An RCT[103] (n=80 diabetic patients with acute coronary syndrome undergoing PCI), assessed the effects of high-dose (80 mg 12 hours prior to surgery and 40mg just before surgery and low dose (10mg at the same times as the high dose group), atorvastatin in preventing CI-AKI. There was no statistically significant difference between either group, in the incidence of CI-AKI.

A meta-analysis[104] (14 RCTs, n = 1689 patients undergoing coronary angiography or PCI) assessed the use of atorvastatin in preventing CI-AKI. The duration of treatment, dosage level or choice of statin was not reported in the abstract. A statistically significant reduction in the incidence of CI-AKI was observed in those receiving high dose atorvastatin, compared with low dose atorvastatin.

Rosuvastatin

A multicentre RCT[105] (n=2998 patients with diabetes and chronic kidney disease) investigated the short-term use (2 days before and days after surgery) of rosuvastatin in preventing post-surgery CI-AKI. The dosage level. This was a gender-based study. There was no significant difference in the incidence of CI-AKI between men and women, in the rosuvastatin group. However there was a significant increase in the incidence of CI-AKI within women in the control group. There was a statistically significant reduction of CI-AKI in women treated with rosuvastatin, compared to the control group. This effect was exaggerated in women with stage 2 chronic kidney disease. Female gender was a statistically significant prognostic factor of CI-AKI.

A meta-analysis[106] (5 RCTs, n= 4045) investigated the effects of rosuvastatin on CI-AKI, compared with placebo. The duration of treatment or dosage level was not reported in the abstract. A statically significant reduction in the risk of CI-AKI, was seen in those receiving rosuvastatin compared with placebo. This effect was not seen in patients who had baseline chronic kidney disease; no significant difference was seen in this group irrespective of rosuvastatin use.

1 study was identified that considered fenoldopam, however this drug is not available in the UK so not discussed further.

1 study was identified that considered carperitide, however this drug is not available in the UK so not discussed further.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence is unlikely to impact on the guideline. The role of statins in preventing CI-AKI is not yet addressed by the guideline. The new evidence seems to suggest that statins, antioxidants and, EPO may have a role in preventing CI-AKI. The evidence of other agents is inconclusive and may require further study in larger studies. Currently, CG169 only discusses the role of ACEI/ARBs in preventing CI-AKI (recommendation 1.2.13). The new evidence demonstrates the effectiveness of short-term statin therapy, prior to cardiac surgery, in reducing the incidence of CI-AKI. However, this is likely to be a desirable secondary outcome of the pharmacological intervention.

NICE is developing a guideline on perioperative care and it was considered that statins in the perioperative context, could be covered in the new guideline. Covering this area in a new guideline on perioperative care would allow for statins and other pharmacological interventions, to be considered for its effects on wider clinical outcomes. Therefore, a new question on pharmacological interventions will not be added.

New evidence is unlikely to impact on the guideline.

NQ – 04 What is the clinical and cost effectiveness of managing acute kidney injury in a primary care setting compared to a secondary/tertiary care setting?

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This question should not be added.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

The topic experts identified two studies of interest:

A qualitative study[107] (40 semi-structured interviews with patients with stage 3 chronic kidney disease, GPs, practice nurses and, community pharmacists) assessed the implementation of 'sick day rules' (i.e. brief stopping of medicines), for the prevention of AKI, in a primary care setting. Sick day rules were seen to consistent with optimal standards of care. However, issues in regards to their implementation were raised. This included: interactions between different services; resources; clarity and consistency of the aims of treatment; dealing with complex/multi-morbid patients.

A prospective cohort study[108] (tertiary referral nephrology unit) assessed the use of an electronic reporting system to diagnose and monitor AKI hospital setting. The electronic reporting system was associated with a low false positive rate, and lower false negative rate. Topic experts provided further information regarding the demographic of the population sampled in this study. A majority of patients acquired AKI in the community.

The topic experts commented that the guideline should be updated to include the management of AKI within the community, primary care setting. They felt that this would allow for ways of avoiding unnecessary admissions to be identified, as well as earlier management of the AKI.

Impact statement

The new evidence is not sufficient to trigger an update, however the topic experts felt that the guideline does not address issues with CA-AKI. The new evidence suggests that there is a greater incidence of AKI in the community, though more severe cases are likely to occur in hospitalised patients. The new evidence also highlighted issues in regards to managing AKI in the community. However due to the lack of robust evidence, the addition of this question will be reviewed again at future surveillance reviews.

New evidence is unlikely to impact on the guideline.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What are the long-term outcomes of acute kidney injury in adults, children and young people?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

RR – 02 What is the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for adults with moderate to severe (stage 2 to 3) acute kidney injury not needing critical care?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 03 Can a simplified definition and staging system, based on SI units, be used to predict short- to medium-term outcomes in acute kidney injury?

No new evidence relevant to the research recommendation was found, however ongoing research relevant to the research recommendation was identified.

The RISK study, assessing risk factors for AKI admission, was expected to complete data collection in 2016.

Surveillance decision

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 04 What is the clinical and cost effectiveness of early versus later introduction of renal replacement therapy in patients with acute kidney injury stages 2 and 3, when there is no urgent need for therapy?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update. Additionally, ongoing research relevant to the research recommendation was found.

The STARRT-AKI trial, comparing standard initiation of RRT to accelerated initiation of RRT, is expected to complete recruitment in 2019.

Surveillance decision

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 05 What is the clinical and cost effectiveness of continuing ACE inhibitor or ARB treatment, versus stopping treatment 24 hours before cardiac surgery

and resuming 24 hours after, in people with chronic kidney disease and an eGFR of less than 30 ml/min/1.73 m2?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee.

RR – 06 In people with CKD and an estimated GFR of less than 30ml/min/1.73m2 on ACEI or ARB therapy, what is the clinical and cost effectiveness of continuing versus stopping this treatment 24 hours 6 before and after administration of iodinated contrast?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 What is the clinical and cost effectiveness of oral rehydration salts versus iv fluids (0.9% saline or 1 sodium bicarbonate) for the prevention of CI-AKI in high risk patients with an estimated GFR of less 2 than 30ml/min/1.73m2 who are receiving iodinated contrast for elective procedures?

New evidence relevant to the research recommendation was found and an update of the related review question is planned.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 08 What is the clinical and cost effectiveness for outpatients with CKD stage 4/5 of an intensive tailored package of advice/care on prevention of AKI versus standard care on outcomes including incidence of AKI, mortality, need for RRT and hospital admission at 3 years?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point..

RR – 09 In acutely ill children what are the indicators for developing AKI?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 10 In children who have had an episode of AKI what are outcomes at 5 years regarding new onset CKD and progression of CKD?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

References

1. Abe D, Sato A, Hoshi T et al. (2014) Clinical predictors of contrast-induced acute kidney injury in patients undergoing emergency versus elective percutaneous coronary intervention. Circulation Journal 78:85-91.
2. Narula A, Mehran R, Weisz G et al. (2014) Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy. European Heart Journal 35:1533-1540.
3. Tong J, Li H, Zhang H et al. (2015) Neutrophil Gelatinase-associated Lipocalin in the Prediction of Contrast-induced Nephropathy: A Systemic Review and Meta-analysis. Journal of Cardiovascular Pharmacology 66:239-245.
4. Zhang A, Cai Y, Wang PF et al. (2016) Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. Critical Care (London, England) 20:41.
5. Afshinnia F, Belanger K, Palevsky PM et al. (2013) Effect of ionized serum calcium on outcomes in acute kidney injury needing renal replacement therapy: secondary analysis of the acute renal failure trial network study. Renal Failure 35:1310-1318.
6. Kiessling AH, Dietz J, Reyher C et al. (2014) Early postoperative serum cystatin C predicts severe acute kidney injury following cardiac surgery: a post-hoc analysis of a randomized controlled trial. Journal Of Cardiothoracic Surgery 9:10.
7. Miller ER, Juraschek SP, Anderson CA et al. (2013) The effects of n-3 long-chain polyunsaturated fatty acid supplementation on biomarkers of kidney injury in adults with diabetes: results of the GO-FISH trial. Diabetes care 36:1462-1469.
8. Chen C, Yang X, Lei Y et al. Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome.
9. Kashani KF, Al-Khafaji AF, Ardiles TF et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.
10. Berwanger O, Cavalcanti AB, Sousa AM 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 6:139-145.

11. Rababa'h AM, Deo S, V, Altarabsheh SE et al. (2016) N-Acetyl Cysteine Therapy Does Not Prevent Renal Failure in High-Risk Patients Undergoing Open-Heart Surgery. Heart Surgery Forum 19:E16-E22.

12. Santana-Santos E, Gowdak LH, Gaiotto FA et al. (2014) High dose of N-acetylcystein prevents acute kidney injury in chronic kidney disease patients undergoing myocardial revascularization. Annals of Thoracic Surgery 97:1617-1623.

13. Sun Z, Fu Q, Cao L et al. (2013) Intravenous N-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. PLoS ONE [Electronic Resource] 8:e55124.

14. Wu MY, Hsiang HF, Wong CS 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 & Nephrology 45:1309-1318.

15. Bailey M, McGuinness S, Haase M et al. (2015) Sodium bicarbonate and renal function after cardiac surgery: a prospectively planned individual patient meta-analysis. Anesthesiology 122:294-306.

16. Dong Y, Zhang B, Liang L 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:e2715.

17. Haase M, Haase-Fielitz A, Plass M et al. (2013) Prophylactic perioperative sodium bicarbonate to prevent acute kidney injury following open heart surgery: a multicenter double-blinded randomized controlled trial. PLoS Medicine / Public Library of Science 10:e1001426.

18. Kim JH, Kim HJ, Kim JY et al. (2015) Meta-Analysis of Sodium Bicarbonate Therapy for Prevention of Cardiac Surgery-Associated Acute Kidney Injury. Journal of Cardiothoracic & Vascular Anesthesia 29:1248-1256.

19. Kooiman J, Sijpkens YW, van B 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 & Haemostasis 12:1658-1666.

20. McGuinness SP, Parke RL, Bellomo R et al. (2013) Sodium bicarbonate infusion to reduce cardiac surgery-associated acute kidney injury: a phase II multicenter double-blind randomized controlled trial.[Erratum appears in Crit Care Med. 2014 Oct;42(10):e691]. Critical Care Medicine 41:1599-1607.

21. Tie HT, Luo MZ, Luo MJ et al. (2014) Sodium bicarbonate in the prevention of cardiac surgery-associated acute kidney injury: a systematic review and meta-analysis. Critical Care (London, England) 18:517.

22. Turner KR, Fisher EC, Hade EM et al. (2014) The role of perioperative sodium bicarbonate infusion affecting renal function after cardiothoracic surgery. Frontiers in Pharmacology 5:127.

23. Zapata-Chica CA, Bello M, D et al. (2015) Sodium bicarbonate versus isotonic saline solution to prevent contrast-induced nephropathy : a systematic review and meta-analysis. Colombia Medica 46:90-103.

24. Zhang B, Liang L, Chen W 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:e006989.

25. Muller RB, Haase N, Lange T et al. (2015) Acute kidney injury with hydroxyethyl starch 130/0.42 in severe sepsis. Acta Anaesthesiologica Scandinavica 59:329-336.

26. Mutter TC, Ruth CA, and Dart AB. (2013) Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database of Systematic Reviews 7:CD007594.

27. Serpa N, A, Veelo DP et al. (2014) Fluid resuscitation with hydroxyethyl starches in patients with sepsis is associated with an increased incidence of acute kidney injury and use of renal replacement therapy: a systematic review and meta-analysis of the literature. Journal of Critical Care 29:185-187.

28. Wilkes MM and Navickis RJ. (2014) Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. Netherlands Journal of Critical Care 18:4-9.

29. Zarychanski R, Abou-Setta AM, Turgeon AF et al. (2013) Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 309:678-688.

30. Cheungpasitporn W, Thongprayoon C, Brabec BA 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 6:618-624.

31. Hiremath S, Akbari A, Shabana W 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 [Electronic Resource] 8:e60009.

32. Serrano AB, Candela-Toha AM, Zamora J et al. (2016) Preoperative hydration with 0.9% normal saline to prevent acute kidney injury after major elective open abdominal surgery. European Journal of Anaesthesiology 33:436-443.

33. Brar SS, Aharonian V, Mansukhani P et al. (2014) Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet 383:1814-1823.

34. Doig GS, Simpson F, Bellomo R et al. (2015) Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. Intensive Care Medicine 41:1197-1208.

35. Su X, Xie X, Liu L et al. (2016) 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 1:1.

36. Yang B, Xu J, Xu F et al. (2014) Intravascular administration of mannitol for acute kidney injury prevention: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 9:e85029.

37. Young P, Bailey M, Beasley R et al. (2015) Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA 314:1701-1710.

38. Awdishu L, Coates CR, Lyddane A et al. (2016) The impact of real-time alerting on appropriate prescribing in kidney disease: A cluster randomized controlled trial. Journal of the American Medical Informatics Association 23:609-616.

39. Wilson FP, Shashaty M, Testani J et al. (2015) Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet 385:1966-1974.

40. Porter CJ, Juurlink I, Bisset LH et al. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital.

41. Wang AY, Bellomo R, Ninomiya T et al. (2014) Angiotensin-converting enzyme inhibitor usage and acute kidney injury: a secondary analysis of RENAL study outcomes. Nephrology 19:617-622.

42. Elgendy IY, Huo T, Chik V et al. (2015) Efficacy and safety of angiotensin receptor blockers in older patients: a meta-analysis of randomized trials. American Journal of Hypertension 28:576-585.

43. Bainey KR, Rahim S, Etherington K et al. (2015) Effects of withdrawing vs continuing renin-angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: Results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial. American Heart Journal 170:110-116.

44. Cheungpasitporn W, Thongprayoon C, Srivali N et al. (2015) Preoperative renin-angiotensin system inhibitors use linked to reduced acute kidney injury: a systematic review and meta-analysis. Nephrology Dialysis Transplantation 30:978-988.

45. Gaudry S, Hajage D, Schortgen F et al. (2016) Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. New England Journal of Medicine 375:122-133.

46. Jamale TE, Hase NK, Kulkarni M et al. (2013) Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. American Journal of Kidney Diseases 62:1116-1121.

47. Xu Y, Gao J, Zheng X et al. (2016) Timing of initiation of renal replacement therapy for acute kidney injury: a systematic review and meta-analysis of randomized-controlled trials. Clinical & Experimental Nephrology 2:2.

48. Zarbock A, Kellum JA, Schmidt C et al. (2016) Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 315:2190-2199.

49. Bei WJ, Duan CY, Chen JY et al. (2016) Remote Ischemic Conditioning for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Interventions/Coronary Angiography: A Meta-Analysis of Randomized Controlled Trials. Journal of Cardiovascular Pharmacology & Therapeutics 21:53-63.

50. Zhang L, Diao Y, Chen G et al. (2016) Remote ischemic conditioning for kidney protection: A meta-analysis. Journal of Critical Care 33:224-232.

51. Zhou C, Jeon Y, Meybohm P et al. (2016) Renoprotection by remote ischemic conditioning during elective coronary revascularization: A systematic review and meta-analysis of randomized controlled trials. International Journal of Cardiology 222:295-302.

52. Zuo B, Wang F, Song Z et al. (2015) Using remote ischemic conditioning to reduce acute kidney injury in patients undergoing percutaneous coronary intervention: a meta-analysis. Current Medical Research & Opinion 31:1677-1685.

53. Hu J, Liu S, Jia P et al. (2016) Protection of remote ischemic preconditioning against acute kidney injury: a systematic review and meta-analysis. Critical Care (London, England) 20:111.

54. Li L, Li G, Yu C et al. (2013) The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis. Journal Of Cardiothoracic Surgery 8:43.

55. Pei H, Wu Y, Wei Y et al. (2014) Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. PLoS ONE [Electronic Resource] 9:e115500.

56. Sardar P, Chatterjee S, Kundu A et al. (2016) Remote ischemic preconditioning in patients undergoing cardiovascular surgery: Evidence from a meta-analysis of randomized controlled trials. International Journal of Cardiology 221:34-41.

57. Walsh M, Whitlock R, Garg A, X et al. (2016) Effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial. CMAJ Canadian Medical Association Journal 188:329-336.

58. Yamanaka T, Kawai Y, Miyoshi T et al. (2015) Remote ischemic preconditioning reduces contrast-induced acute kidney injury in patients with ST-elevation myocardial infarction: a randomized controlled trial. International Journal of Cardiology 178:136-141.

59. Yang Y, Lang XB, Zhang P et al. (2014) Remote ischemic preconditioning for prevention of acute kidney injury: a meta-analysis of randomized controlled trials. American Journal of Kidney Diseases 64:574-583.

60. Zhang Y, Zhang X, Chi D et al. (2016) Remote Ischemic Preconditioning for Prevention of Acute Kidney Injury in Patients Undergoing On-Pump Cardiac Surgery: A Systematic Review and Meta-Analysis. Medicine 95:e3465.

61. Zarbock A, Schmidt C, Van A et al. (2015) Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA 313:2133-2141.

62. Deftereos S, Giannopoulos G, Tzalamouras V et al. (2013) Renoprotective effect of remote ischemic post-conditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. Journal of the American College of Cardiology 61:1949-1955.

63. Garg A, X, Kurz A, Sessler D, I et al. (2014) Perioperative aspirin and clonidine and risk of acute kidney injury: a randomized clinical trial. JAMA 312:2254-2264.

64. Nawa T, Nishigaki K, Kinomura Y et al. (2015) Continuous intravenous infusion of nicorandil for 4 hours before and 24 hours after percutaneous coronary intervention protects against contrast-induced nephropathy in patients with poor renal function. International Journal of Cardiology 195:228-234.

65. Bayram A, Ulgey A, Baykan A et al. (2014) The effects of dexmedetomidine on early stage renal functions in pediatric patients undergoing cardiac angiography using non-ionic contrast media: a double-blind, randomized clinical trial. Paediatric Anaesthesia 24:426-432.

66. Cai J, Xu R, Yu X et al. (2014) Volatile anesthetics in preventing acute kidney injury after cardiac surgery: a systematic review and meta-analysis. Journal of Thoracic & Cardiovascular Surgery 148:3127-3136.

67. Gordon AC, Mason AJ, Thirunavukkarasu N et al. (2016) Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA 316:509-518.

68. Hu Y, Li Z, Chen J et al. (2013) The effect of the time interval between coronary angiography and on-pump cardiac surgery on risk of postoperative acute kidney injury: a meta-analysis. Journal Of Cardiothoracic Surgery 8:178.

69. Patel NN and Angelini GD. (2014) Pharmacological strategies for the prevention of acute kidney injury following cardiac surgery: an overview of systematic reviews. Current Pharmaceutical Design 20:5484-5488.

70. Thamcharoen N, Thongprayoon C, Edmonds PJ et al. (2015) Periprocedural Nebivolol for the Prevention of Contrast-Induced Acute Kidney Injury: A Systematic Review and Meta-analysis. North American Journal of Medical Sciences 7:446-451.

71. Nigwekar SU, Strippoli GF, and Navaneethan SD. (2013) Thyroid hormones for acute kidney injury. Cochrane Database of Systematic Reviews 1:CD006740.

72. Jacob KA, Leaf DE, Dieleman JM et al. (2015) Intraoperative High-Dose Dexamethasone and Severe AKI after Cardiac Surgery. Journal of the American Society of Nephrology 26:2947-2951.

73. Scrascia G, Guida P, Rotunno C et al. (2014) Anti-inflammatory strategies to reduce acute kidney injury in cardiac surgery patients: a meta-analysis of randomized controlled trials. Artificial Organs 38:101-112.

74. Rezaei Y, Khademvatani K, Rahimi B et al. (2015) Short-term high-dose vitamin e to prevent contrast medium-induced acute kidney injury in patients with chronic kidney disease undergoing elective coronary angiography: A randomized placebo-controlled trial. Journal of the American Heart Association 5 (3) (no pagination).

75. Sadat U, Usman A, Gillard JH et al. (2013) Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography: a systematic review with meta-analysis of randomized, controlled trials. Journal of the American College of Cardiology 62:2167-2175.

76. Wang XT, Yan J, Li L et al. (2014) Anti-oxidative vitamin for the prevention of contrast-induced acute kidney injury in patients with chronic kidney disease: Meta-analysis of randomized controlled trials. Experimental and Clinical Cardiology 20:1385-1410.

77. Penny-Dimri JC, Cochrane AD, Perry LA et al. (2016) Characterising the Role of Perioperative Erythropoietin for Preventing Acute Kidney Injury after Cardiac Surgery: Systematic Review and Meta-Analysis. Heart, Lung & Circulation 16:16.

78. Tie HT, Luo MZ, Lin D et al. (2015) Erythropoietin administration for prevention of cardiac surgery-associated acute kidney injury: a meta-analysis of randomized controlled trials. European Journal of Cardio-Thoracic Surgery 48:32-39.

79. Zhao C, Lin Z, Luo Q et al. (2015) Efficacy and Safety of Erythropoietin to Prevent Acute Kidney Injury in Patients With Critical Illness or Perioperative Care: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Journal of Cardiovascular Pharmacology 65:593-600.

80. Chionh CY, Soni SS, Finkelstein FO et al. (2013) Use of peritoneal dialysis in AKI: a systematic review. Clinical Journal of The American Society of Nephrology: CJASN 8:1649-1660.

81. Clark E, Molnar AO, Joannes-Boyau O et al. (2014) High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis. Critical Care (London, England) 18:R7.

82. Fayad A, I, Buamscha D et al. (2016) Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database of Systematic Reviews .

83. Gallagher M, Cass A, Bellomo R et al. (2014) Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Medicine / Public Library of Science 11:e1001601.

84. Mc C, Finnian R, Asafu-Adjei J et al. (2016) Comparison of Urine Output among Patients Treated with More Intensive Versus Less Intensive RRT: Results from the Acute Renal Failure Trial Network Study. Clinical Journal of The American Society of Nephrology: CJASN 11:1335-1342.

85. Park JT, Lee H, Kee YK et al. (2016) High-Dose Versus Conventional-Dose Continuous Venovenous Hemodiafiltration and Patient and Kidney Survival and Cytokine Removal in Sepsis-Associated Acute Kidney Injury: A Randomized Controlled Trial. American Journal of Kidney Diseases 68:599-608.

86. Schefold JC, von H, S et al. (2014) The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Critical Care (London, England) 18:R11.

87. Schneider AG, Bellomo R, Bagshaw SM et al. (2013) Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Medicine 39:987-997.

88. Barbieri L, Verdoia MF, Schaffer AF et al. The role of statins in the prevention of contrast induced nephropathy: a meta-analysis of 8 randomized trials.

89. Cheungpasitporn W, Thongprayoon CF, Kittanamongkolchai WF et al. Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and meta-analysis of randomized controlled trials.

90. Gandhi S, Mosleh W, Abdel-Qadir H et al. (2014) Statins and contrast-induced acute kidney injury with coronary angiography. American Journal of Medicine 127:987-1000.

91. Giacoppo D, Capodanno D, Capranzano P et al. (2014) Meta-analysis of randomized controlled trials of preprocedural statin administration for reducing contrast-induced acute kidney injury in patients undergoing coronary catheterization. American Journal of Cardiology 114:541-548.

92. Lee JM, Park J, Jeon KH et al. (2014) Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomized controlled trials. PLoS ONE [Electronic Resource] 9:e111397.

93. Li H, Wang C, Liu C et al. (2016) Efficacy of Short-Term Statin Treatment for the Prevention of Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Angiography/Percutaneous Coronary Intervention: A Meta-Analysis of 21 Randomized Controlled Trials. American Journal of Cardiovascular Drugs 16:201-219.

94. Li M, Zou H, and Xu G. (2016) The prevention of statins against AKI and mortality following cardiac surgery: A meta-analysis. International Journal of Cardiology 222:260-266.

95. Marenzi G, Cosentino N, Werba JP et al. (2015) A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. International Journal of Cardiology 183:47-53.

96. Pan SY, Wu VC, Huang TM et al. (2014) Effect of preoperative statin therapy on postoperative acute kidney injury in patients undergoing major surgery: systemic review and meta-analysis. Nephrology 19:750-763.

97. Singh N, Lee JZ, Huang JJ et al. (2014) Benefit of statin pretreatment in prevention of contrast-induced nephropathy in different adult patient population: Systematic review and meta-analysis. Open Heart 1 (1) (no pagination).

98. Thompson K, Razi R, Lee MS et al. (2016) Statin use prior to angiography for the prevention of contrastinduced acute kidney injury: A meta-analysis of 19 randomised trials. EuroIntervention 12:366-374.

99. Ukaigwe A, Karmacharya P, Mahmood M et al. (2014) Meta-analysis on efficacy of statins for prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography. American Journal of Cardiology 114:1295-1302.

100. Xie H, Ye Y, Shan G et al. (2014) Effect of statins in preventing contrast-induced nephropathy: an updated meta-analysis. Coronary Artery Disease 25:565-574.

101. Haynes R, Lewis D, Emberson J et al. (2014) Effects of lowering LDL cholesterol on progression of kidney disease. Journal of the American Society of Nephrology 25:1825-1833.

102. Billings FT, Hendricks PA, Schildcrout JS et al. (2016) High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery: A Randomized Clinical Trial. JAMA 315:877-888.

103. Galal H, Nammas W, and Samir A. (2015) Impact of high dose versus low dose atorvastatin on contrast induced nephropathy in diabetic patients with acute coronary syndrome undergoing early percutaneous coronary intervention. Egyptian Heart Journal 67:329-336.

104. Wu H, Li D, Fang M et al. (2015) Meta-analysis of short-term high versus low doses of atorvastatin preventing contrast-induced acute kidney injury in patients undergoing coronary angiography/percutaneous coronary intervention. Journal of Clinical Pharmacology 55:123-131.

105. Li J, Li Y, Xu B et al. (2016) Short-term rosuvastatin therapy prevents contrast-induced acute kidney injury in female patients with diabetes and chronic kidney disease: A subgroup analysis of the TRACK-D study. Journal of Thoracic Disease 8:1000-1006.

106. Yang Y, Wu Y, X, and Hu YZ. (2015) Rosuvastatin Treatment for Preventing Contrast-Induced Acute Kidney Injury After Cardiac Catheterization: A Meta-Analysis of Randomized Controlled Trials. Medicine 94:e1226.

107. Morris RL, Ashcroft D, Phipps D et al. Preventing Acute Kidney Injury: a qualitative study exploring 'sick day rules' implementation in primary care.

108. Selby NM, Crowley LF, Fluck RJ FAU - McIntyre C et al. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients.