**Acute kidney injury: prevention, detection and management: summary of updated NICE guidance for adults receiving iodine-based contrast media**

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**Abstract**  
The National Institute for Health and Care Excellence has recently updated the guideline for “Acute kidney injury: prevention, detection and management” (NG148), providing new recommendations on preventing acute kidney injury (AKI) in adults receiving intravenous iodine-based contrast media.   
  
The association between IV iodinated contrast and AKI is controversial, particularly with widespread use of iso-osmolar agents. Associations between contrast administration and AKI are largely based on observational studies, with inherent heterogeneity in patient populations, definitions applied, and timing of laboratory investigations. In an attempt to mitigate risk, kidney protection has typically been employed using IV volume expansion and/or oral acetylcysteine. Such interventions are in widespread use, despite lacking high-quality evidence of benefit.   
  
In the non-emergency setting, Glomerular Filtration Rate (GFR) measurements should be obtained within the preceding 3 months before offering IV iodine-based contrast media. In the acute setting, adults should also have their risk of AKI assessed before offering IV iodine-based contrast, however, this should not delay emergency imaging. Based on the evidence available from randomised controlled trials, the NICE committee recommends that oral hydration should be encouraged in adults at increased risk of CI-AKI and that volume expansion with IV fluids should only be considered for inpatients at particularly high risk.

**Introduction**This article summarises recent recommendations from the update of the National Institute for Health and Care Excellence (NICE) guideline for Acute kidney injury: prevention, detection and management (NG148) (1). This guideline updates and replaces NICE guideline CG169 (August 2013) and specifically includes new and updated recommendations on preventing acute kidney injury (AKI) in adults receiving iodine-based contrast media.  
  
*Why did the guidance need updating?*The main catalyst for the update was the publication of new randomised trials adding to the evidence considered for the 2013 guideline. The AMACING study (2) compared the effectiveness of no prophylaxis to intravenous (IV) volume expansion with 0.9% sodium chloride, in patients referred for diagnostic or interventional elective procedures requiring intravascular-iodinated contrast material and considered at high risk of subsequently developing AKI. The results showed non-inferiority of either treatment. The subsequent PRESERVE trial (3) comparing bicarbonate and/or N-acetylcysteine (NAC) to intravenous 0.9% sodium chloride and/or placebo in high-risk patients undergoing angiography showed no difference in outcome between regimes. These new trials were seen as potentially sufficient to change existing recommendations, thus a decision was made to update this part of the guideline with the aim of assessing the clinical and cost effectiveness of NAC and/or fluids in preventing AKI in at risk adults undergoing procedures involving iodine-based contrast media.

**Background**The terminology and definitions used to describe acute kidney injury following iodinated contrast media are varied and often employed inter-changeably. AKI is a sudden reduction in kidney function that occurs within a few hours or days, and is defined in the guideline according to the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) definition (4-6); **Table 1**. AKI following administration of iodinated contrast has previously been referred to as contrast induced nephropathy (CIN). The terminology employed by NICE follows the proposals of the KDIGO international guidelines, namely contrast-induced AKI (CI-AKI). The time frame at which CI-AKI develops is typically accepted as being 48 - 72 hours after exposure to an iodinated contrast agent, when alternative explanations for reduced kidney function have been excluded. The American College of Radiology (ACR) and European Society of Urogenital Radiology (ESUR) prefer the term “post-contrast acute kidney injury” (PC-AKI) or “contrast-associated acute kidney injury” (CA-AKI) (7, 8). CA-AKI is considered a correlative diagnosis, whereas CI-AKI implies a direct causative relationship to the administration of iodinated contrast media, and is considered a subtype of CA-AKI. The casual relationship of “contrast-induced” AKI may not always be clearly established, due to medical co-morbidity and it can be challenging to prove alternative causes, leading to the preference of the umbrella terms CA-AKI or PC-AKI. Furthermore, as CI-AKI is defined based on laboratory measurements alone, any adverse effects on patient-centred outcomes are not apparent (9).

**Incidence**The association between intravenous iodinated contrast media and AKI is controversial, particularly as the use of high-osmolar contrast media is now largely outdated, with replacement by low and iso-osmolar agents (10). Risk is further reduced by trends towards reduced doses of iodinated-media and low kilovoltage peak (kVp) CT techniques that are afforded by modern scanners, and in patients with very low Glomerular Filtration Rate (GFR), the consideration of alternative investigations, including ultrasound, MRI, or unenhanced CT. The incidence of CI-AKI varies greatly in the literature, with studies typically being observational and largely retrospective in nature. There is marked heterogeneity in patient populations, definitions applied, and timing of laboratory investigations. It should also be noted that prospective randomised controlled trials may often include heterogeneous patient groups or include patients receiving iodinated agents for interventional rather than diagnostic purposes (2, 3). Interventional procedures administer variable doses of iodinated contrast, may involve an intra-arterial administration with first-pass to the renal vessels, and typically include patients who are in an older age-group and more likely to have co-morbidity, including diabetes.  
  
The incidence of AKI post iodinated contrast in patients with normal kidney function is estimated at 1 - 2% (11), occurring within 72 hours and usually recovering within five days. Conversely, CI-AKI may be as high as 30% in patients with risk factors that include reduced kidney function, co-morbidity or concurrent exposure to nephrotoxic drugs (12). However, small rises in serum creatinine have been shown in 8 - 35% of patients admitted to hospital without exposure to iodinated contrast agents (13). Of direct relevance to this, a single-centre retrospective study of more than 60,000 emergency department patients showed no difference in the incidence of AKI in patients undergoing contrast-enhanced CT, unenhanced CT, or no CT, at 6.8%, 8.9%, and 8.1%, respectively (14).   
  
A recent meta-analysis, incorporating 26 observational studies and more than 100,000 patients, found no increased incidence of AKI, need for dialysis, or mortality between patients receiving contrast-enhanced CT versus those undergoing non-contrast CT (9). However, patients were not randomized to receive contrast or no contrast and there may have been bias in selecting some patients for unenhanced CT due to a greater baseline risk of AKI. Indeed, multivariable analyses have identified reduced kidney function as the only risk factor predictive of CI-AKI (15). In an attempt to mitigate risk, kidney protection has typically been employed using IV volume expansion (sodium bicarbonate or normal saline) and/or with oral acetylcysteine. Such interventions are in widespread use, despite lacking high-quality evidence of benefit. The largest study investigating NAC showed no benefit in reducing AKI or other clinically relevant outcomes in at-risk patients undergoing coronary or peripheral angiography (16). The PRESERVE study confirmed no benefit of NAC over placebo administration and showed equivalence between IV administration of sodium bicarbonate (1.26%) and sodium chloride (0.9%) (3). The AMACING study showed non-inferiority of oral hydration to IV sodium chloride (0.9%), in patients considered at high risk for developing AKI (estimated GFR 45–60 ml/min/m2), and with a significant increase risk of developing heart failure in the IV hydration group (2).

**Evidence review**The review question posed was: What is the comparative clinical and cost effectiveness of N-acetylcysteine and/or fluids in preventing CI-AKI in at risk adults? This evidence review was developed using the methods and process described in “Developing NICE guidelines: the manual” (17). A systematic search was carried out to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, including adult patients (18 and older) who are at risk (as defined by the study author) of CI-AKI (1). AKI definition and timing was study-defined, but usually taken to occur at 48 - 72 hours post-contrast administration, but could be diagnosed within up to 7 days, to allow for delays in testing. The intervention was determined to be administration of sodium chloride, sodium bicarbonate, oral fluids, NAC, other IV fluids, or combinations of above interventions, with the comparators being to each other, to placebo (for NAC), or to no treatment. Outcome measures included chronic kidney disease (CKD) progression (**Table 2.**) at 3 months after diagnosis of CI-AKI, mortality (up to 1 year), number of patients needing renal replacement therapy, and adverse events (including heart failure). The review identified 70 RCTs reporting 17 interventions/comparators that fulfilled the conditions (**Figure 1.**).  
 **Network Meta-analysis**  
Hierarchical Bayesian Network Meta-Analysis (NMA) was performed to synthesise evidence from all RCTs and provide estimates of the comparative effectiveness of all possible approaches. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis (18). A modified version of the standard GRADE approach for pairwise interventions (19, 20) was used to assess the evidence across the NMA. The quality of the evidence was judged to be low. The main reason for downgrading was risk of bias of the included studies (lack of detailed report of the randomisation process, lack of report that protocols were pre-registered, and either participants were aware of which intervention were assigned or the assignment of interventions was not well described).

The NMA included 17 interventions/comparators which can be seen in the network diagram (**Figure 2.**). The evidence from the NMA suggested that CI-AKI rates can be expected to be broadly similar across interventions, although uncertainty intervals were broad (**Figure 3.**). None of the intravenous regimens had superior results to oral hydration. Sodium chloride 0.9% and sodium bicarbonate appeared to be equivalent for preventing CI-AKI, but sodium chloride 0.45% was associated with worse outcomes. There was limited evidence for other outcomes and subgroup analyses from the pairwise data. Based on this evidence and economic evidence (see below), the committee made ‘consider’ recommendations. The committee did not feel able to make strong recommendations because the evidence was low quality for the NMA.  
 **Economic modelling**There were no published economic evaluations identified that were relevant to the review question, so an original economic model was developed to help answer the question from a cost effectiveness perspective (1).  
  
The economic model allowed two subgroups to be analysed – people undergoing elective scans who are assumed to have a low risk of CI-AKI, and people being treated in emergency inpatient settings who are likely have a higher risk of CI-AKI. For these high-risk inpatients, cost-effectiveness results showed that IV volume expansion with a regimen containing IV sodium chloride 0.9% and/or IV sodium bicarbonate provides best value. In the non-acute setting, model results suggested that IV fluids for preventing CI-AKI do not represent good value for money (1). Therefore, the committee recommended the use of oral hydration in these patients. On this basis, the committee agreed that there is no justification for admitting outpatients into hospital for the sole purpose of administering IV prior to procedures involving iodine-based contrast media. The new recommendations may result in lower resource use and costs for outpatient procedures given the reduced need for patients to be admitted to hospital for pre-hydration with IV fluids before being given contrast medium. There may also be reduced use of resources for lower-risk inpatients who will not require IV pre-hydration.  
 **Recommendations**Recommendations relating to the prevention of AKI in at-risk adults undergoing procedures involving iodine-based contrast media were updated (**Table 3**), while remaining recommendations from the 2013 guideline were retained, including sections on assessing risk of AKI, detection and management. For adults on renal replacement therapy, including those with a kidney transplant, the patient’s care and options for alternative imaging investigations should be discussed with the nephrology team before proceeding with investigations involving iodinated contrast media; however, emergency imaging should not be delayed for such discussions as clinical need will take precedence. Retained from the 2013 version of the guideline was the recommendation to consider temporarily stopping angiotensin converting enzyme (ACE) inhibitors, and/or angiotensin II receptor antagonists (ARBs) in adults having iodine-based contrast media if they have CKD (eGFR <40 ml/min/1.73 m2).   
In the non-emergency setting, adults should be investigated for CKD by measuring eGFR or by reviewing an eGFR result obtained within the preceding 3 months before offering IV iodine-based contrast media. The committee agreed that volume expansion with IV fluids is not necessary for outpatients who are usually at a lower risk of CI-AKI. For adults considered at increased risk of CI-AKI (**Table 4**), oral hydration should be encouraged before and after procedures using IV iodine-based contrast media. The committee highlighted the importance of adequate hydration in people having IV iodine based contrast media. However, no specific type of oral hydration is recommended in this context as this will depend on volume status and fluid balance, and some pre-existing medical conditions, thus the aim of oral hydration should be to achieve euvolaemia.  
  
In the acute setting, adults should have their risk of AKI assessed before offering IV iodine-based contrast media; however, this should not delay emergency imaging. For inpatients having iodine-based contrast media, IV volume expansion with either isotonic sodium bicarbonate or 0.9% sodium chloride should be considered if patients are deemed to be at particularly high risk (**Table 4**). Of note, the risk associated with intra-arterial administration of iodinated agents depends on the site of the injection, and is considered of higher risk with first-pass kidney exposure when contrast medium passes into the kidneys relatively undiluted, for example injection into the left heart, thoracic and suprarenal abdominal aorta, or directly into the renal arteries. The guideline committee concluded that there was equivalency between sodium bicarbonate (1.26%) and 0.9% sodium chloride; however, 0.45% sodium chloride appeared to be less effective, and so was not recommended. There was limited evidence suggesting NAC is beneficial; however, in the absence of evidence of harm, the committee did not explicitly recommend restriction and its future role was posed as a research question (see below). For patients with other medical contraindications to receiving IV fluids, the committee agreed that the decision to give iodine-based contrast media in those deemed at higher risk should be made by the responsible healthcare professional.  
  
**Future research Questions posed by NICE**As part of the 2019 update, the guideline committee made 2 new research recommendations:  
[1] Risk stratification for contrast-induced acute kidney injury:  
*- Can risk of contrast-induced acute kidney injury be stratified by eGFR thresholds?*  
[2] Different oral fluids and oral fluid regimens:  
*- What is the relative effectiveness and cost effectiveness of different oral fluids and different oral fluid regimens, both with and without oral N-acetylcysteine, at preventing contrast-induced acute kidney injury?*

**Relevant perspective**Independent to this review, the American College of Radiology and the US National Kidney Foundation conducted an assessment of the risks of contrast-induced nephropathy in patients with CKD and came to broadly similar conclusions in a consensus statement (21). **Summary**The updated NICE guideline for Acute kidney injury: prevention, detection and management (NG148) specifically includes new and updated recommendations on preventing AKI in adults receiving iodine-based contrast media. Based on the evidence available from RCTs and a health economic model, the committee recommends that oral hydration should be encouraged in adults at increased risk of CI-AKI and that volume expansion with IV fluids should only be considered for inpatients at particularly high risk. The committee agreed that more research on estimating the risk of CI-AKI would help to inform future guidance, and made a research recommendation on the use of eGFR thresholds to stratify risk.

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**Figure Legends  
  
Figure 1. Clinical evidence study selection  
Figure 2. Network diagram.**Line thickness represents the number of studies. **Figure 3. Forest plot comparing intervention to no hydration**

**Tables**

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| **Criteria for Acute Kidney Injury** |
| * Rise in serum creatinine of ≥26 micromol/litre within 48 hours or * ≥50% rise in serum creatinine known or presumed to have occurred within the past 7 days or * Fall in urine output to <0.5 ml/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people or * ≥25% fall in eGFR in children and young people within the past 7 days |

**Table 1. Definitions of acute kidney injury**eGFR = estimated Glomerular Filtration Rate.

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| **Stage** | **eGFR (ml/min/1.73m2)** | **Description** | **Qualifier** |
| 1 | ≥90 | Kidney damage, normal or increased GFR | Kidney damage (presence of structural abnormalities and/or persistent haematuria, proteinuria or microalbuminuria) for ≥3 months |
| 2 | 60-89 | Kidney damage, mildly reduced GFR |
| 3A | 45-59 | Moderately reduced GFR ± other evidence of kidney damage | GFR <60 ml/min for ≥3 months ± kidney damage |
| 3B | 30-44 |
| 4 | 15-29 | Severely reduced GFR ± other evidence of kidney damage |
| 5 | <15 | Established kidney failure |

**Table 2.** **Stages of chronic kidney disease**  
eGFR = estimated Glomerular Filtration Rate.

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| **Recommendations for preventing AKI in adults receiving IV iodine-based contrast media** |
| * Routine use of IV volume expansion is not routinely recommended in **outpatients** undergoing investigations with IV iodine based contrast media * Encourage **oral hydration** before and after procedures using IV iodine based contrast media in adults at increased risk of CI-AKI *(see Table 4)* * For **inpatients** having IV iodine-based contrast media, consider IV volume expansion with either isotonic sodium bicarbonate or 0.9% sodium chloride if they are at particularly high risk *(see Table 4)* * Consider temporarily stopping ACE-i and ARBs in adults having IV iodine-based contrast media if CKD with an eGFR <40 ml/min/1.73m2 [2013] * Discuss the patient's care with a nephrology team before offering iodine-based IV contrast media to adults on renal replacement therapy, including people with a renal transplant, but do not delay emergency imaging for this |

**Table 3.** **Summary of updated NICE recommendations on preventing AKI in adults receiving iodine-based contrast media.** IV = intravenous; CI-AKI = contrast-induced acute kidney injury; ACE- I = angiotensin converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; CKD = chronic kidney disease; eGFR = estimated Glomerular Filtration Rate.

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| **Adults considered at increased risk for developing AKI [2013]** |
| * CKD with an eGFR less <40 ml/min/1.73m2 * Diabetes but only with CKD (if eGFR <40 ml/min/1.73m2 then considered at particularly high risk) * Heart failure * Age 75 years or over * Hypovolaemia |
| **Adults considered at particularly high risk for developing AKI [2019]** |
| * eGFR <30 ml/min/1.73m2 * Renal transplant patients * A large volume of contrast medium is being used (for example, higher than the standard diagnostic dose or repeat administration within 24 hours) * Intra-arterial administration of contrast medium with first-pass renal exposure is being used\* |

**Table 4. Patients considered at increased and particularly high risk of developing AKI.** CKD = chronic kidney disease; eGFR = estimated Glomerular Filtration Rate.\*First-pass renal exposure = contrast medium reaches the renal arteries relatively undiluted (e.g. injection into the left heart, thoracic and suprarenal abdominal aorta, or directly into the renal arteries).