## Intensive care medicine and renal transplantation 1

# Management of patients at risk of acute kidney injury

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**Acute kidney injury (AKI) is a multifaceted syndrome that occurs in different settings. The course of AKI can be variable, from single hit and complete recovery, to multiple hits resulting in end-stage renal disease. No interventions to improve outcomes of established AKI have yet been developed, so prevention and early diagnosis are key. Awareness campaigns and education for health-care professionals on diagnosis and management of AKI—with attention to avoidance of volume depletion, hypotension, and nephrotoxic interventions—coupled with electronic early warning systems where available can improve outcomes. Biomarker-based strategies have not shown improvements in outcome. Fluid management should aim for early, rapid restoration of circulatory volume, but should be more limited after the first 24–48 h to avoid volume overload. Use of balanced crystalloid solutions versus normal saline remains controversial. Renal replacement therapy should only be started on the basis of hard criteria, but should not be delayed when criteria are met. On the basis of recent evidence, the risk of contrast-induced AKI might be overestimated for many conditions.**

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This is the first in a **Series** of two papers about intensive care medicine and kidney transplantation

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## Introduction

Acute kidney injury (AKI) is a clinical syndrome that is associated with many conditions. Interventional treatments for established AKI have been disappointing. Although renal replacement therapy (RRT) is the mainstay of treatment for advanced AKI, RRT is potentially harmful and not readily available in all settings and regions. Awareness of and care for patients with AKI are suboptimal.[1] In most cases AKI is attributable to simple causes such as volume depletion, hypotension, and exposure to nephrotoxic medications.[2] Accordingly, attention has shifted in the past decade from treatment to prevention, early detection, and proactive management of AKI to avoid further damage in the short term and long term. AKI is often a continuum of kidney injury rather than a single-hit, freestanding condition (figure 1). Chronic kidney disease (CKD) is an important risk factor in AKI development and AKI in turn predisposes patients to CKD.

This Series paper will describe the strategies used to identify patients at risk of AKI and assess the potential effect of management strategies that aim to decrease the effect of nephrotoxicity and improve outcomes.

### Search strategy and selection criteria

We searched MEDLINE and the Cochrane database of Systematic Reviews for articles published between Jan 1, 2010, and Sept 31, 2016, without language restrictions. We used MeSH terms and key words for acute kidney injury and fine-tuned this search according to the following topics using appropriate boolean operators: biomarkers, risk prediction models, prevention, statins, electronic alerts, ischaemic preconditioning, and early start. We primarily included publications from the past 5 years. Articles not retrieved by the search that were regarded as highly relevant by the authors were added to the reference list (for full search strategy see appendix).

## Identification of patients at risk and early diagnosis of AKI

Risk prediction for and early identification of AKI are key in the attempt to reduce the burden of AKI.[3] Prevention should not only apply to patients with a generic increased risk of AKI (table 1), but also to patients with impending and even established AKI to avoid additional kidney damage or delay in recovery. For patients at increased risk of AKI and those with impending and established AKI, use of interventions

### Key messages

- Acute kidney injury (AKI) is a preventable condition, but implementation of current preventive strategies is suboptimal.
- Education and awareness of AKI should be improved for non-nephrologist health-care providers.
- AKI is a continuum, and prevention of additional damage to an already injured kidney is crucial.
- Patients who have recovered from AKI should be followed up because some might have an accelerated course of chronic kidney disease.
- Avoidance of nephrotoxicity and volume depletion is key for prevention of AKI in patients in hospital.
- Use of electronic alerts—eg, when serum creatinine values rise—for identification of patients at high-risk of AKI and for drug-dose adaptations are useful if these alerts are coupled to a specific course of action and awareness campaigns in the framework of a care bundle.
- For prevention of contrast-induced AKI, patients at intermediate risk might benefit from oral volume expansion schedules. In high-risk patients, intravenous volume expansion is preferable.

See **Online** for appendix

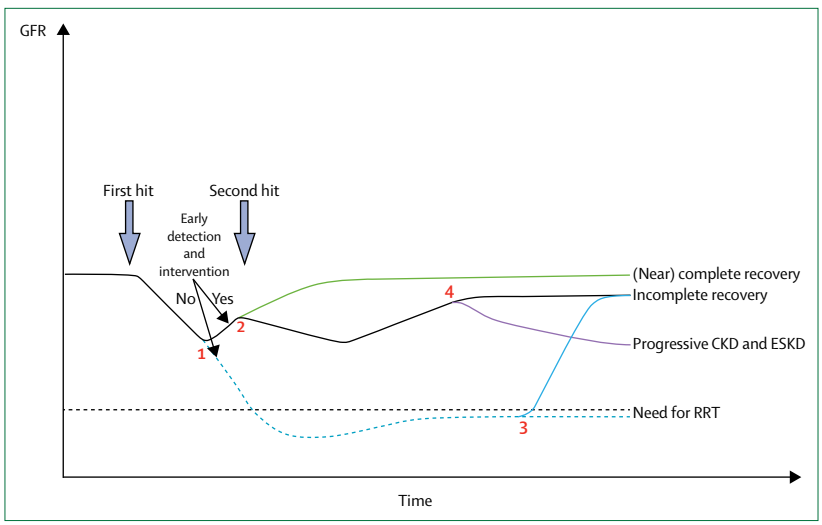


***Figure 1:*** **The course of AKI over time**
(1) Preventive action can be taken when acute kidney injury (AKI) is discovered at an early stage, and progression to the need for renal replacement therapy (RRT; dotted blue line) can potentially be avoided (full black line). (2) During recovery from AKI, the kidneys are more susceptible to further injury, which can result in new deterioration of renal function (full black line) rather than recovery (green line). (3) Patients can recover their kidney function after starting RRT (full blue line). This recovery is often incomplete, which can result in progressive chronic kidney disease (CKD) and eventually end-stage kidney disease (ESKD; full lilac line). (4) Patients who have had a second AKI hit rarely recover their kidney function completely (full blue line), and have an increased risk of progressive CKD and evolution to ESKD over time (full lilac line). GFR=glomerular filtration rate.

that are potentially nephrotoxic should be balanced against their expected benefit.

The course, severity, and outcome of AKI can be very different from patient to patient and from situation to situation (figure 1). This variation is determined by the presence or absence of pre-existing underlying CKD (acute episode in chronically ill patients *vs* acute episode in previously healthy patients) and thus the initial GFR; early detection and intervention (or not); and additional nephrotoxic insults by drugs, hypotension, contrast media, post renal causes, or infections. In the best case (single hit in a previously healthy patient), kidney function recovers completely; however, presence of underlying chronic kidney disease, repetitive insults, and inadequate detection or intervention can contribute to incomplete recovery, which can lead to progressive CKD and need for chronic RRT.

## Risk prediction

Many risk prediction scores for AKI have been described (see table 1 for externally validated scores and appendix for all risk prediction scores). Most are limited to a specific setting, so cannot be generalised outside that setting. Even within a specific setting, heterogeneity between populations can jeopardise the validity of risk prediction. External validation in large multicentre cohorts is thus necessary before risk prediction models can be adapted in clinical practice. In the post cardiac surgery population, the Cleveland Clinic Score provides reasonably accurate predictions of RRT, but validated scores predicting AKI without the need for RRT are scarce. In the setting of major non-cardiovascular surgery, most risk prediction models for AKI lack data on the effect of their clinical implementation.[4] A predictive score for AKI was developed from a large database of routinely measured variables in a general ward population with AKI incidence of 8·6%; internal validation showed a sensitivity of 82% and a specificity of 65%, but external validation has not yet been checked.[5]

## AKI diagnostic classification criteria

Despite criticism,[6] the introduction of diagnostic classification criteria for AKI has been a major step forward. The KDIGO[7] diagnostic criteria for AKI can be considered as a combination of the RIFLE[8] and AKIN[9] criteria. KDIGO also defined the concept of acute kidney disease, which encompasses not only AKI, but also conditions with persistent signs of renal damage for more than 7 days and less than 90 days after the initial insult, or conditions that do not fulfil the classic AKI criteria.

## Functional markers of AKI

The diagnostic classification criteria for AKI still rely on functional markers of kidney activity such as glomerular filtration rate (GFR) and urinary output. Currently, an increase in serum creatinine is used as a surrogate measure for a decrease in GFR. However, the relationship between serum creatinine concentration and GFR is not linear, and serum creatinine only starts to rise when GFR has already decreased substantially. Dilution due to fluid overload, decreased creatinine generation due to reduced food intake, and decreased muscle activity or sepsis can further increase the delay in serum creatinine increase after onset of AKI. Furthermore, the relationship between the clinical course and the pathology of AKI is not well understood. In a study by Chu and colleagues,[10] many patients with histological evidence for AKI did not fulfil the clinical criteria for AKI or acute kidney disease, mainly because the serum creatinine increase was slower than the rate of increase required to meet the AKI definition.

Early detection of AKI through monitoring of urinary output is predictive of development of later AKI and is associated with mortality.[11,12] In patients with sepsis, oliguria flags up impending AKI before detectable tubular injury occurs.[13] Assessment of urinary output in 6 h blocks is as effective as continuous urinary monitoring for prediction of AKI,[11] and could be done in general wards, where the gain of early AKI awareness has most potential. Discriminative value of urinary output for evolution of AKI can be enhanced by use of the furosemide stress test, in which furosemide (1·0 or 1·5 mg/kg) is administered intravenously as a bolus. If the urinary output response is less than 100 mL over the following 2 h, both the risk for progression to

stage 3 AKI and need for RRT increases. Furosemide binds to albumin and is actively secreted into the tubular lumen in the proximal convoluted tubule, so furosemide-induced increase in urinary output can show the integrity of renal tubular function.[14] The furosemide stress test outperforms urinary biomarkers in predicting the development of stage 3 AKI, the need for RRT, and inpatient mortality.[15]

## Urinary biomarkers

The search for a troponin-like biomarker indicative of tubular damage, allowing earlier diagnosis of AKI

| | Outcome derivation cohort | Derivation model population | Derivation model | | | |
|---|---|---|---|---|---|---|
| | | | Sample size | Events | Discrimination AUC ROC | Calibration HL goodness of fit p value |
| **Cardiac surgery** | | | | | | |
| Thakar et al (2005), Cleveland Clinic Score | AKI requiring RRT | Cardiac ± valve surgery | 15 838 | 269 | 0·81 (0·78–0·83) | NR |
| Mehta et al (2006), STS score | AKI requiring RRT | CABG ± valve surgery | 449 524 | 6451 | 0·84 | HL not significant |
| Chertow et al (1997), CICSS | AKI requiring RRT | Cardiac ± valve surgery | 42 733 | 460 | 0·76 | NR |
| Wijeysundera et al (2007), Simplified Renal Index | AKI requiring RRT | Cardiac surgery using CPB | 10 751 | 139 | 0·81 (0·78–0·84) | 0·27 |
| Brown et al (2007), NNECDSG | Severe renal insufficiency defined as eGFR <30 mL/min per 1·73 m² after surgery | Isolated CABG, exclusion of patients with eGFR <60 mL/min per 1·73 m² | 8363 | 229 | 0·72 (0·68–0·75) | 0·28 |
| Pannu et al (2016) | AKI requiring RRT | Cardiac surgery | 6061 | 154 | 0·87(0·85–0·90) | 0·7 |
| Palomba et al (2007), AKICS | Increase in sCr above 176·8 µmol/L (baseline <132·6 µmol/L) or increase of 50% (baseline 132·6–265·2 µmol/L) | Elective CABG ± valvular surgery | n=603 | 66 | 0·84 (0·78–0·89) | 0·8 |
| Jorge-Monjas et al (2006), CRATE | AKI according to RIFLE | Cardiac surgery with CPB | 810 | 137 | 0·89 (0·85–0·92) | 0·16 |
| Ranucci et al (2009), ACEF | Mortality | Elective cardiac operation | 4557 | 150 | 0·74 (0·70–0·79) | 0·791 |
| **Contrast-induced AKI** | | | | | | |
| Mehran et al (2004), MRS | sCr increase >44·2 µmol/L or 25% increase from baseline within 48 h of PCI | PCI | 5571 | 729 | 0·69 sCr, 0·70 eGFR | 0·43 sCr, 0·42 eGFR |
| Bartholomew et al, (2004) | ≥88·4 µmol/L increase in sCr from baseline within 48 h of PCI | PCI | 10 481 | 293 | 0·89 | 0·10 |
| Maioli et al (2010) | >44·2 µmol/L sCr increase from baseline within 5 days after PCI | Coronary angiography or PCI | 1218 | 114 | 0·86 | NR |
| Marenzi et al (2004) | >44·2 µmol/L sCr increase from baseline within 48 h after PCI | PCI for STEMI | 208 | 40 | NR | NR |
| Tziakas et al (2013) | >44·2 µmol/L sCr increase or 25% increase from baseline within 48 h after PCI | Elective or emergency PCI | 488 | 50 | 0·76 | 0·50 |
| Tsai et al (2014) | AKI according to AKIN criteria | PCI | 662 504 | 48 818 | 0·71 (0·709–0·717) for AKI, 0·88 for AKI+RRT | Calibration slope 1·001 for AKI and 0·99 for AKI+RRT |
| Brown et al (2008) | Serious renal dysfunction=new onset of dialysis, ≥176·8 µmol/L increase in sCr from baseline, or ≥50% increase in sCr from baseline | PCI | 11 141 | 83 | 0·87 (0·82–0·91) | 0·51 |

(Table 1 continues on next page)

| | Outcome derivation cohort | Derivation model population | Derivation model | | | |
|---|---|---|---|---|---|---|
| | | | Sample size | Events | Discrimination AUC ROC | Calibration HL goodness of fit p value |
| (Continued from previous page) | | | | | | |
| **Heart failure** | | | | | | |
| Forman et al (2004) | >26·5 µmol/L sCr increase | Patients admitted to hospital with heart failure | 1004 | 273 | NR | NR |
| **Liver surgery** | | | | | | |
| Utsumi et al (2013) | RIFLE criteria | Living donor liver transplantation | 200 | 121 | NR | NR |
| Slankamenac et al (2009) | AKIN criteria | Any type of liver resection | 380 | 58 | 0·8 full model, 0·77 reduced model | 0·75 for the reduced model |
| **General surgery** | | | | | | |
| Kheterpal et al (2009) | AKI defined as an increase in sCr of >176·8 µmol/L from preoperative value or RRT need within 30 days of surgery | Major surgical procedures (excluding vascular, cardiac, urology, ophthalmology, paediatric, or obstetric) | 57 080 | 561 | 0·80 (0·79–0·81) | NR |
| **Orthopaedic surgery** | | | | | | |
| Bell et al (2015) | AKI according to KDIGO (based on sCr only) | Orthopaedic surgery | 6220 | 672 | 0·74 (0·72–0·76) | Calibration slope 1·0 |
| **Rhabdomyolysis** | | | | | | |
| McMahon et al (2013) | AKI according to KDIGO (based on sCr only) | CPK >5000 IU within 72h of admission | 1397 | 281 | 0·82 (0·80–0·85) | 0·14 |

See appendix for all available risk prediction models and studies listed. AUC ROC=area under receiver operating characteristic. HL=Hosmer-Lemeshow. AKI=acute kidney injury. RRT=renal replacement therapy. NR=not reported. STS=Society of Thoracic Surgeons. CABG=coronary artery bypass graft. CICSS=Continuous Improvement in Cardiac Surgery Study. CBP=cardiopulmonary bypass. NNECDSG=Northern New England Cardiovascular Disease Study Group. eGFR=estimated glomerular filtration rate. AKICS=acute kidney injury prediction following elective cardiac surgery. sCr=serum creatinine. CRATE=creatinine, lactic acid, cardiopulmonary bypass time, Euroscore. RIFLE=risk, injury, failure, loss of kidney function, and end-stage kidney disease. ACEF=age, creatinine, and rejection fraction. MRS=Mortality Risk Score. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. AKIN=Acute Kidney Injury Network. KDIGO=Kidney Disease Improving Global Outcomes. CPK=creatine phosphokinase.

***Table 1:*** **Externally validated risk prediction models for AKI**

compared with the classic measurements, has been a top priority. These biomarkers reflect either damage to tubular cells (eg, N-acetyl β glucosaminidase, glutathione S transferase, and alkaline phosphatase), podocytes, or structural parts of the kidney (eg, F actin and sodium–hydrogen exchanger 3); or enhanced inflammatory crosstalk in the kidney (eg, interleukins 18, 6, 10, and 5), upregulation of genes in response to AKI (such as neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1), decreased proximal tubular reabsorption (eg, retinol binding protein, cystatin C and $\beta_2$ microglobulin) or markers of cell cycle arrest (eg, tissue inhibitor metalloproteinase-2 [TIMP-2] and insulin-like growth factor binding protein-7 [IGFBF-7]). Use of proteomics has facilitated development of panels of biomarkers to increase diagnostic accuracy.[16] Biomarkers do not always translate usefully from the research setting to clinical practice[17] for different reasons. AKI is often not a single hit at a well defined timepoint; the window of opportunity is mostly short, and differs between biomarkers, so timing of sampling becomes troublesome and nearly continuous sampling might be required. None of the biomarkers are specific for kidney disease and all biomarkers can be increased by other underlying causes, irrespective of the presence of kidney damage. Because it is unclear how much damage is clinically relevant, the diagnostic threshold for these biomarkers is unknown; improvements in diagnostic sensitivity by use of biomarkers compared with existing criteria might just reflect false positive results.

Whether reported thresholds are relevant in all conditions, irrespective of age, sex, other comorbidities, and eventual presence of underlying chronic kidney damage, is uncertain. Furthermore, technical issues remain in sampling, storage, and handling of samples. The test methods for measuring biomarkers need to be validated and standardised, and the effect of issues such as antibody configuration of the test clarified.

Whereas initial studies with NGAL in the well defined setting of paediatric cardiac surgery were promising,[18] later studies did not show an improvement in diagnostic performance over existing criteria.[19,20]

NGAL is associated with inflammation so is not useful in patients with sepsis.[21,22] In the Acute Kidney Injury NGAL Evaluation of Symptomatic Heart Failure Study (AKINESIS),[23] plasma NGAL was not superior to serum creatinine for predicting AKI stage 2 or poor in-hospital outcome in patients with decompensated heart failure.

Cell cycle inhibitors appear to be an early signal of renal injury. When cells are injured they respond by shutting down and arresting their cell cycle to avoid cell death and inflammation. Several large studies in critically ill patients underlined the role of these biomarkers for prediction of KDIGO stage 2 and 3 AKI.[24] The US Food and Drug Administration (FDA) approved the use of [TIMP-2]*[IGFBP-7], but stressed that the use of these markers is not a standalone test for KDIGO stage 2 or 3 AKI and should not be used at point of care.[25] Concerns about the usefulness of [TIMP-2]*[IGFBP-7] for AKI prediction remain because these markers are influenced by several other comorbidities[26] and do not outperform clinical measures.[15] Only when biomarkers have clearly been shown to outperform a standard clinical model and improve patient outcomes will they be ready for implementation in clinical practice. Only a handful of studies have incorporated biomarkers as a clinical decision aid or risk stratification tool and results from these studies have been inconsistent.[27–30]

## Imaging techniques

The need for non-invasive tools to aid in (differential) diagnosis, prediction of recovery, and unravelling of the pathophysiology of AKI, have led to renewed interest in ultrasound and functional MRI techniques.

Doppler resistive index (RI) has been used in different settings for prediction of AKI as well as for identification of prerenal azotaemia and for assessment of AKI severity, and has shown promising results.[31–33] Changes in renal perfusion can be assessed in different pathological conditions by use of contrast-enhanced ultrasonography (CEUS), which allows organ blood quantification. This technique might allow assessment of renal perfusion in response to different therapeutic actions.[34,35]

Several functional MRI techniques such as blood oxygen level dependent (BOLD), arterial spin labelling (ASL), and ultrasmall superparamagnetic iron oxide particle (USPIO) MRI have also gained interest.[36] These non-invasive techniques, which allow simultaneous evaluation of renal morphology and renal function, are based on the paramagnetic properties of deoxyhaemoglobin (BOLD), magnetic labelling of water protons (ASL), and administration of superparamagnetic iron particles (USPIO).[36] BOLD MRI has been used in patients with allografts to differentiate between acute tubular necrosis and acute rejection; however, studies have shown inconsistent results.[37,38] ASL[39] assesses renal perfusion, USPIO[40] measures inflammation, and BOLD MRI reflects tissue oxygen bioavailability—although it cannot differentiate between changes in oxygen delivery (renal blood flow), oxygen consumption (sodium transport), and efficiency of oxygen use. BOLD MRI works on the assumption that tissue oxygen levels are in equilibrium with, and proportional to, blood oxygen levels, but this premise has been questioned.[41] Furthermore, no standardised method to analyse renal BOLD MRI data exists.[42] Doppler RI and CEUS have several shortcomings as well.[43–45] RI measurement is affected by numerous confounding factors such as changes in intrarenal compliance, renal interstitial pressure, heart rate, and intra-abdominal pressure.[46,47] Although CEUS can indicate substantial changes in cortical perfusion, interobserver variability is high and responses among patients are heterogeneous, unpredictable, and have an unclear relationship with patient characteristics.[47]

Before these imaging techniques can be used in clinical practice, larger studies in different settings and patient groups, with standardisation of techniques, are needed.

## Electronic automated early warning systems

Care in AKI is often suboptimal and many opportunities for AKI prevention are missed.[1] Although early nephrology involvement seems beneficial,[48,49] non-nephrologists should also be educated about AKI since they are most likely to be the first or main health-care professionals involved in care for patients with AKI.[50] Electronic automated early warning systems for AKI are being developed and implemented. Such systems require two essential steps: detection and alerting. Detecting algorithms differ in the type of data (eg, sex, age, and change of serum creatinine), the extent of data sources (data collected during hospital admission or previous data from external sources), and the decision support rules they use. This heterogeneity results in varying sensitivity, specificity, accuracy, and robustness. Alerting systems can be passive (eg, a pop up in the health record), active (a text message requiring reading confirmation), or even interruptive (patient data cannot be used further until action is taken). Furthermore, the alert should be accompanied by clear instructions on what action to take in response to the alert and implementation of automated warning systems should also include education and awareness campaigns. Differences in approach for these steps might explain why some systems work[51] and others do not;[52] an AKI care bundle including the use of electronic alert systems improved in-hospital mortality rates and reduced odds for AKI deterioration,[51] whereas an electronic alerting system used without well structured instructions on how to follow up an alert did not change practice and thus failed to improve patient outcomes.[52]

| | Effect on AKI incidence | Evidence for effect | Comments |
|---|---|---|---|
| **Contrast-induced AKI** | | | |
| Ascorbic acid | Protective | Low quality | .. |
| Probucol | Protective | Low quality | Data restricted to percutaneous coronary intervention setting |
| Methylxanthine | Protective | Low quality | .. |
| Statins | Protective | Intermediate quality | .. |
| Device-guided matched volume expansion | Protective | Low quality | Low quality evidence for positive effect on mortality and need for RRT |
| Prostaglandins | Protective | Low quality | Data limited to setting of percutaneous coronary intervention |
| Trimetazidine | Protective | Low quality | Data restricted to percutaneous coronary intervention setting |
| N-acetylcysteine plus saline | Protective | Intermediate quality | Affects tubular secretion of creatinine giving false positive improvement in creatinine-based definitions of AKI; data inconclusive in cystatin C based studies |
| Fenoldopam | Protective | Low quality, conflictive | .. |
| Nebivolol | Protective | Low quality | Very limited data |
| Mannitol | Protective | Low quality | .. |
| Natriuretic peptide | Protective | Low quality | Data restricted to percutaneous coronary intervention setting |
| Furosemide | Negative | Low quality | .. |
| LVEDP guided volume expansion | Protective | Low quality | .. |
| Dopamine or fenoldopam | No effect | High quality | Potential harm by arrhythmias and hypotension |
| **Perioperative major non-vascular surgery** | | | |
| Diuretics | No effect | Low quality | .. |
| Calcium channel blockers | No effect | Low quality | .. |
| Angiotensin-converting enzyme blockers | No effect | Low quality | No effect when started de novo; conflicting data from patients on chronic maintenance therapy who stop treatment; increased risk from continuing maintenance therapy in older patients and those with underlying CKD; all observational data |
| Clonidine | No effect | High quality | .. |
| Aspirin | No effect | High quality | .. |
| N-acetylcysteine | No effect | Low quality | Effect on tubular secretion of creatinine |
| Atrial natriuretic peptide | Protective | Low quality | Majority of data from one study at high risk of bias |
| Erythropoietin | Unclear | Low quality | .. |
| Statins | No effect | Intermediate quality | High heterogeneity among studies |
| **Perioperative cardiovascular surgery** | | | |
| Levosimendan | Unclear | Low quality | .. |
| Erythropoietin | No effect | Low quality | .. |
| Dexamethasone | Protective | Low quality | Single trial, low event rates, effect greatest in eGFR <15mL/min per 1·73 $m^2$; number needed to treat 160 |
| Atrial natriuretic peptide | No effect | Low quality | Does not decrease RRT-requiring AKI nor mortality |
| Statins | Conflictive results | High quality | Continuing statin likely to be safe; starting statin probably associated with higher AKI risk |
| Diuretics | No effect | Low quality | .. |
| N-acetylcysteine | No effect | Low quality | .. |
| **Intensive care unit** | | | |
| Insulin growth factor | No effect | Low quality | .. |
| Fenoldopam | Conflictive | Low quality | Potential harmful effects |
| Alkaline phosphatase | Potentially positive | Low quality | Large trial ongoing |

AKI=acute kidney injury. RRT=renal replacement therapy. LVEDP=left ventricular end-diastolic pressure. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate.

***Table 2:*** **Interventions for prevention of AKI**

## Preventive interventions

In patients at risk, preventive measures should be taken to avoid renal injury or prevent further injury progression (figure 1). So far, only volume loading for the prevention of contrast-induced AKI and avoidance of drugs that might contribute to AKI have proven to be of value, whereas results for other strategies are inconclusive or indicate potential harm (table 2).

## Optimisation of volume status

Restoration and maintenance of adequate systemic and renal perfusion are key, and can be achieved by administration of fluids and vasoactive drugs. However, patients with early-stage AKI are at increased risk of developing fluid overload because of oliguria. Fluid overload is associated with increased mortality in patients with AKI and does not contribute to restoration of kidney function. Thus, a conflict exists between adequate fluid resuscitation in hypotension and the harmful consequences of fluid overload.[53] In any case over zealous administration of intravenous fluids should be avoided. Changes in fluid status can be independent, and even occur in opposite directions, in the interstitial space and intravascular compartment. Correct assessment and monitoring of volume status is a major challenge.

Early goal-directed therapy can prevent organ failure and improve patient survival.[54] Implementation of protocolised haemodynamic management strategies aiming to achieve central venous pressures of 8–12 mm Hg rapidly, and more restricted fluid loading later on, are recommended.[7,55] Three large randomised trials[56–58] in patients with early septic shock did not show benefit from early goal-directed therapy versus control. However, mortality was substantially lower in the treatment groups than in the control group in the study by Rivers and colleagues,[54] suggesting that key components such as rapid and adequate fluid resuscitation and haemodynamic management have already become standard care and led to an overall reduction in mortality.

### *Assessment of fluid status*

Whereas oedema should be checked for in the ankles of all patients, the thighs and buttocks should also be assessed in those who are bedridden. Presence of oedema does not exclude intravascular volume depletion. Oliguria can indicate reduced renal perfusion. The use of central venous pressure and pulmonary artery catheters to assess volume status are debated in critically ill patients because they do not predict the response to a fluid challenge[59] or improve outcome in the general intensive care unit (ICU) population.[60] Pulse wave and pulse contour analysis allows continuous monitoring of cardiac output and beat-to-beat variations after administration of a fluid bolus or during a passive leg raise test, and their use might improve outcomes in patients undergoing high-risk surgery.[61] In patients who are critically ill and on a mechanical ventilator, dynamic measures such as stroke volume variation and pulse pressure variation can be used to identify hypovolaemia and fluid responsiveness. Pulmonary congestion can be a sign of genuine fluid overload in the circulating compartment or of a failing heart. Volume depletion in the circulating compartment can be assessed by ultrasonographic measurement of the diameter and collapsibility of the inferior vena cava.[62]

### *Type of fluid to administer*

Colloid solutions theoretically provide a longer duration of plasma expansion compared with a similar volume of crystalloid solutions. Randomised trials investigating the use of crystalloids or colloids as the primary source of volume resuscitation found no difference (albumin *vs* crystalloid in the SAFE trial),[63] no difference in mortality but higher need for RRT with colloids (hydroxyethylstarch *vs* crystalloids in the CHEST study),[64] or increased mortality with hydroxyethylstarch versus Ringer's lactate (in the 6S Trial).[65] In a meta-analysis,[66] hydroxyethylstarch was associated with an increase in mortality, AKI incidence, and use of RRT. Therefore, the European Medicines Agency and the FDA have issued warnings against the use of hydroxyethylstarch solutions in patients who are critically ill, and their use is now (correctly) no longer recommended.

Excess levels of chloride in 0·9% saline solutions might have adverse effects on acid–base homoeostasis and renal function. In observational studies[67] a chloride-restrictive strategy in patients who were critically ill was associated with reduced incidence of AKI and need for RRT, although these results were not confirmed in a recent trial[68] in a general ICU population (including mostly postsurgery patients). However as rather limited amounts of fluids were applied, the recent trial might have been false negative.

## Avoidance of nephrotoxicity and further insult

AKI is often iatrogenic. Use of drugs that can contribute to AKI, either directly or by inducing AKI through haemodynamic factors, should be scrutinised, especially in patients at high risk (eg, older patients, those with volume depletion, or patients taking a combination of non-steroidal anti-inflammatory drugs [NSAIDs], diuretics, and renin-angiotensin-aldosterone system [RAAS] blockers).[69] The duration and dose of exposure should be minimised and, if appropriate, therapeutic drug monitoring should be done (eg, in patients given vancomycin or aminoglycosides). Electronic alerts can increase awareness of these dangerous combinations. Of note, even topical NSAIDs increase the risk of AKI.[70]

The argument that RAAS blockers should be stopped in the perioperative setting or in cases of intercurrent illness is controversial. In observational studies, an association between continuing RAAS inhibitor treatment preoperatively and reduced AKI incidence is only found when the analysis is restricted to studies with propensity matching and not in the overall patient group.[71] The effect on AKI incidence of stopping rather than continuing RAAS inhibitor treatment in the perioperative period will be assessed in a systematic review.[72] In the setting of cardiac surgery,[73] temporarily stopping treatment with RAAS blockers prevented AKI associated with cardiac surgery. Continuation versus

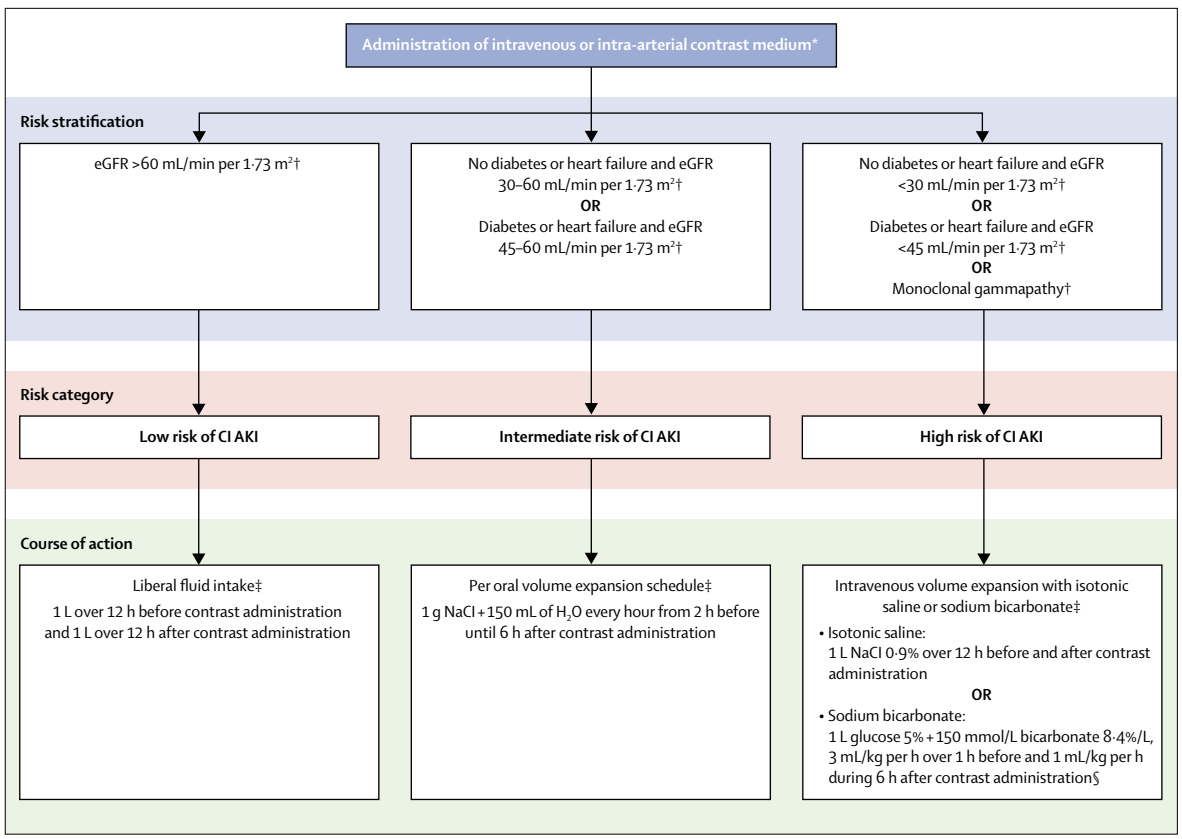


***Figure 2:*** **Flowchart for prevention of contrast-induced (CI) AKI**
Several reports indicate that the risk of CI-AKI is similar in intra-arterial and intravenous contrast medium administration. eGFR=estimated glomerular filtration rate. NaCl=sodium chloride. *Use the lowest possible volume of contrast. There is no evidence for preference of low osmolar over iso-osmolar isotonic contrast medium. †Avoid contrast administration in patients with monoclonal gammapathies (relative contraindication). ‡Avoid repetitive contrast administration (<7 days after previous contrast administration). Reschedule if possible in case of recent (ie, within 72 h) use of non-steroidal anti-inflammatory drugs. There is no consensus on whether renin-angiotensin-aldosterone system blockers or diuretics should be stopped prior to contrast administration. Metformin should be stopped 48 h before the procedure and restarted 72 h after the procedure in high-risk patients. §Maximum rate of 300 mL/h before and 100 mL/h after contrast administration. Consider reducing fluid rate by half in patients with New York Heart Association class III or IV heart failure.

temporary suspension of treatment with RAAS inhibitors[74] was associated with a higher incidence of contrast-induced AKI, an effect more pronounced in older patients and in those with pre-existing chronic kidney disease. Stopping of RAAS inhibitor treatment can be promoted provided the RAAS inhibition is restarted after the intervention.[75]

Intensity of glycaemic control in the perioperative phase and in patients in the ICU has been a matter of controversy. Early single-centre studies showed that glycaemic control reduced mortality and incidence of AKI, but later multicentre trials did not confirm these findings.[76] Because long-term benefits of strict glycaemic control are offset by the risk of hypoglycaemia, modest glycaemic control—ie, achieving serum glucose concentration of 8·3–10·0 mmol/L—is the preferred strategy.

Many interventions for prevention of contrast-induced AKI have shown inconsistent results except for fluid loading with water and salt (table 2) and the use of small volumes of contrast media. Whereas hyperosmolar contrast media should be avoided, there is insufficient evidence to prefer the use of iso-osmolar over low-osmolar contrast media for prevention of contrast-induced AKI.[7,55] For intravenous fluid administration, the use of bicarbonate is not superior to normal saline in prevention of this form of AKI.[77] Controversy remains about the appropriate schedule for volume expansion, especially in patients with heart failure, in whom the increased risk of AKI should be balanced against increased risk of hypervolaemia. Devices that aim to titrate the infusion rate to urinary output during volume expansion report seemingly promising results, but have often used suboptimal control strategies.[78–81] Short, rapid volume expansion with sodium bicarbonate before contrast-enhanced CT was non-inferior to peri-procedural saline volume expansion,[82] which is an important observation in view of logistics and costs in the ambulatory setting; oral fluids for volume expansion suffice in most patients receiving intravenous contrast.[83,84] However, only two-thirds of patients at risk of contrast-induced AKI are

sufficiently volume expanded before contrast administration.[85] To improve precontrast hydration while safeguarding logistical challenges and costs, a step-up approach with oral fluid protocols for low-risk patients and intravenous fluid protocols for high-risk patients should be promoted (figure 2).[86]

Meta-analyses suggest a beneficial role for statins in the prevention of contrast-induced AKI[87] in the setting of coronary intervention, but the results might not be generalisable to other settings. The beneficial effect of statins in prevention of contrast-induced AKI is not consistent in patients with CKD.[88,89] The greatest reductions in contrast-induced AKI was observed when patients were treated with N-acetylcysteine (NAC) plus intravenous saline and with statins plus NAC and intravenous saline,[90] but the role of NAC is debated because it also increases tubular secretion of creatinine and thus impairs assessment of changes in serum creatinine.

A study[91] using data from the Nation Wide Inpatient Sample demonstrated that risk of contrast-induced AKI might be overestimated, confirming previous reports.[92] Depending on the underlying condition, the absolute risk of AKI attributable to contrast administration varied from modest to non-existent. In non-adjusted models risk of AKI was, for most conditions, even lower in patients who received contrast, compatible with the concept that physicians avoid using contrast in patients with more comorbidities because of the perceived risk of AKI. The low risk of AKI attributable to contrast administration suggests such a strategy might not be warranted in many conditions. However, the risk of contrast-induced AKI is not zero, and therefore this risk should always be balanced against the consequences of an incomplete diagnostic or interventional work-up caused by avoiding contrast administration.

### Interventions to prevent (further) damage

Despite much research in AKI in the past decades, no candidate molecules have successfully translated from animal models to human beings. Because AKI can be the result of various insults, the likelihood of finding one substance for the prevention and treatment of the various forms of AKI is low. Alpha-melanocortin stimulating hormone receptor agonist (ABT-719), for example, has anti-inflammatory effects, but in a phase 2b trial[93] ABT-719 treatment did not lower AKI incidence, affect concentrations of novel biomarkers, or change 90-day outcomes in patients after cardiac surgery. The most promising treatment for AKI in patients with sepsis is the recombinant human alkaline phosphatase, which is currently being tested in a phase 2b study.[94]

Several other interventions have either been controversial or not beneficial (table 2). The use of dopamine for AKI prevention has been abandoned, data on the efficacy of fenoldapam provide conflicting results,[95] and mixed results have been shown for natriuretic peptides in AKI prevention.[96,97] The rationale for use of statins in the perioperative period is a pleiotropic effect, but they have not been effective in human beings[98] and increases in serum concentrations of creatinine and AKI incidence have been reported in patients treated de novo with atorvastatin or rosuvastatin.[99,100]

Low-quality evidence indicates a beneficial effect of levosimendan for prevention of AKI in cardiac surgery;[101] although the addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality than in those not given levosimendan.[102] Recently, neither perioperative clonidine nor aspirin prevented AKI in non-cardiovascular surgery, possibly because the negative impact of the side-effects (hypotension with clonidine, and bleeding due to aspirin use) could not overcome the small positive effects.[103]

### Non-pharmacological means to prevent AKI

Limb remote ischaemic preconditioning (RIPC) activates endogenous protective mechanisms against injury by ischaemia-reperfusion in distant organs, including the kidney. In a multicentre study in patients undergoing on-pump cardiac surgery, RIPC was induced by inflation of a blood pressure cuff applied to one of the patient's upper arms to 200 mm Hg for 5 min, followed by 5 min reperfusion, for three cycles. This intervention reduced the incidence of AKI within 72 h after the operation and the use of RRT, and TIMP-2 plus IGFBP-7 and NGAL were lower in the RIPC group than in the control group 4–24 h postoperatively.[104] However, these results were not reproduced in two multicentre studies in cardiac surgery.[105,106] A systematic review[107] showed a benefit of RIPC for contrast-induced AKI but not for ischaemia-induced AKI. Confounding variables, such as patient characteristics and ischaemic preconditioning protocols, might explain these conflicting results.

## Starting time of renal replacement therapy in AKI

For some conditions, such as pulmonary oedema or severe hyperkalaemia not responsive to conservative therapy, RRT can be life-saving. For all other situations, the start time of RRT is a matter of ongoing debate because data seem to conflict. Confusingly, different studies use time factors, biochemical factors, or clinical characteristics to define early versus late start of RRT. In an observational cohort,[108] early start of RRT was associated with higher mortality than late start of RRT and lower versus higher serum creatinine to define early or late start of RRT (criterion based), whereas assessment on the basis of duration of ICU stay (time based) showed that early start of RRT was associated with lower mortality than late start of RRT. Because most studies have used a criterion-based approach rather than a time-based

approach, it might be better to use the terminology immediate start versus delayed start of RRT to indicate the relation of the timing of RRT with the moment a certain criterion has been met, rather than the terminology early versus late. In a meta-analysis no benefit of immediate start of RRT was observed when randomised trials were included, whereas observational cohort studies showed a 28% risk reduction in mortality, with a high risk for publication bias.[109] Two recent large trials presented conflicting results. The single centre ELAIN study,[30] which assessed patients in ICU with AKI stage 2 and with either severe sepsis or refractory fluid overload, showed that immediate initiation of RRT reduced 90-day mortality compared with delayed start of RRT (44 of 112 patients in the immediate RRT initiation group *vs* 65 of 119 patients in the delayed RRT initiation group, hazard ratio 0·66, 95% CI 0·45–0·97). The immediate group started RRT (100%) within 8 h of inclusion, whereas the delayed group started within 12 h of reaching AKI stage 3 (91%); only 9% of patients in this group did not start RRT—so in reality, this protocol tested the effect of delaying RRT in a patient group with a clear indication for renal replacement. The multicentre Artificial Kidney Initiation in Kidney Injury study (AKIKI)[110] included patients in ICU who were critically ill needing pressors or invasive ventilation with AKI stage 3, but excluded patients who had a hard indication for RRT at eligibility screening. In the early initiation group RRT was started immediately after inclusion, whereas in the late initiation group start of RRT was delayed until one of the well defined hard criteria for starting RRT was met. In effect, this study compared start of RRT based on KDIGO stage 3 AKI criteria versus start of RRT based on existing hard indications. In this setting, no advantage for immediate start compared with delayed start of RRT was observed (mortality at 60 days was 150 of 311 patients *vs* 153 of 308 patients). In the delayed start group, 49% of patients did not start RRT at all, and recovery of residual diuresis was faster, and the occurrence of line infection was lower than in patients in the immediate start group (5% *vs* 10% of patients). This finding indicates that a too precocious start of RRT is not helpful, and might contribute further damage to an already injured kidney. Given the vast heterogeneity of underlying clinical scenarios and complications that patients with AKI have, doubts remain about whether this clinical dilemma can eventually be solved by decisive randomised trials. Instead, a practical way to improve clinical care might lie in the development of algorithms that provide a framework of specific recommendations to assist clinicians in their individual decision making.[111]

## CKD after AKI

Many patients who develop AKI will not have any follow-up of their kidney function, although the risks of recurrent AKI are well known.[112] Over the past decade, evidence has accumulated suggesting that severe AKI predisposes patients to faster progression of CKD later on—especially if they have had multiple hits of AKI or have pre-existing CKD (figure 1).[112] Therefore, it is important that patients are actively involved in the preservation of their kidney health and postdischarge follow-up of kidney function is organised.

**Contributors**

All authors contributed to writing the manuscript, discussing its content, and designing the tables and figures. JV performed the search strategies and the data extraction for tables 1 and 2. All authors have read and approved the final submitted version.

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