Contrast-induced acute kidney injury: potential new strategies

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Purpose of review
Contrast-induced acute kidney injury (CI-AKI) is an impairment of renal function following contrast media administration in the absence of an alternative cause. It represents a powerful predictor of poor early and late outcomes. Here, we review the major strategies to prevent CI-AKI.

Recent findings
Hydration represents the gold standard as a prophylactic measure to prevent CI-AKI, acting by increasing urine flow rate and, thereby, by limiting the time of contact between the contrast media and the tubular epithelial cells. An optimal hydration regimen should be defined according to predefined clinical markers, such as urine flow rate, or left ventricular end-diastolic pressure. Recently, high-dose statins pretreatment has been included in the guidelines of CI-AKI prevention. However, uncertainty still exists on the efficacy of several compounds tested in both observational trials and randomized studies to prevent CI-AKI. Compounds evaluated include diuretics (furosemide), antioxidants (i.e. N-acetylcysteine and statins) and vasodilators (i.e. calcium antagonists, dopamine and fenoldopam).

Summary
Hydration still represents the most reliable strategy to prevent CI-AKI. New prophylactic strategies for acute kidney injury are still under investigation.

Keywords
antioxidant, iodinated contrast media, nephrotoxicity, prevention

INTRODUCTION

Iodinated contrast media are usually well tolerated; however, in some patients, they may induce acute kidney injury (AKI). Contrast-induced AKI (CI-AKI) accounts for approximately 10% of all causes of hospital-acquired renal failure, causes a prolonged in-hospital stay and represents a powerful predictor of poor early and late outcome. CI-AKI is defined as an impairment of renal function following contrast media administration in the absence of alternative causes [1]. Moreover, patients developing CI-AKI are at a higher risk of both a further deterioration of kidney function and an unfavourable clinical outcome [2]. On the basis of the possible mechanisms of CI-AKI, different strategies have been proposed to prevent this complication. This review is focused on the therapeutic strategies and the molecular basis to prevent CI-AKI.

MOLECULAR MECHANISMS OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

Hypoxia, vasoconstriction and cytotoxic effects are the main adverse consequences of contrast media administration. However, the molecular mechanisms underlying CI-AKI have not been completely elucidated.

A toxic effect of contrast media on renal tubules has been shown in both clinical trials and animal experiments [3–6]. We and others provided evidence that contrast media induce renal cell apoptosis [7–10] in a dose and time-dependent manner [8,11]. We observed that the cytotoxic effect, although maximum at 3 h, was mostly (≈85%) observed within 15 min of incubation. This finding highlights the importance of strategies limiting the

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KEY POINTS

- Identification of patients at risk.
- Description of the pathophysiology of CI-AKI.
- Evaluation of the prophylaxis of CI-AKI.

exposure of the kidney to the toxins contained in the contrast agent by generating high urine flow in patients.

Studies in humans indicate that reactive oxygen species (ROS) contribute to CI-AKI [10,12,13]. ROS activate c-Jun N-terminal kinases (JNK 1/2), and p38MAPK stress kinases, which contribute to the activation of caspase-9 and caspase-3 and thus of the apoptotic process (Fig. 1) [8,14,15].

CONTRAST-INDUCED ACUTE KIDNEY INJURY DEFINITION

Serum creatinine (sCr) is still considered the major marker of CI-AKI. The sCr typically peaks 2–5 days after contrast media exposure and returns to baseline or near baseline within 1–3 weeks [16,17]. The current recommendations for the diagnosis of CI-AKI are reported in Table 1.Therefore, in all patients at risk, a follow-up sCr should be obtained at 48–72 h following contrast media exposure [16–19]. This implies an intrinsic delay of treatment of patients who will develop CI-AKI, and, conversely, prolonged hospitals stay in patients who will not develop CI-AKI. Moreover, sCr levels often underestimate the kidney damage. In fact, creatinine excreted in the urine is not solely a result of glomerular filtration but also of renal tubular secretion [20]. This means that changes in sCr will underestimate the true fall in glomerular filtration rate (GFR). Therefore, although the injury induced by contrast media impairs the GFR almost immediately, it requires 24–48 h for the fall in GFR to be reflected in an elevated sCr. Due to these limitations, other biomarkers have been considered and others are under investigation. Cystatin C increases earlier (within 24 h) than sCr [21,22]. The biomarker most investigated in the setting of CI-AKI is neutrophil gelatinase associated lipocalin (NGAL). NGAL, a

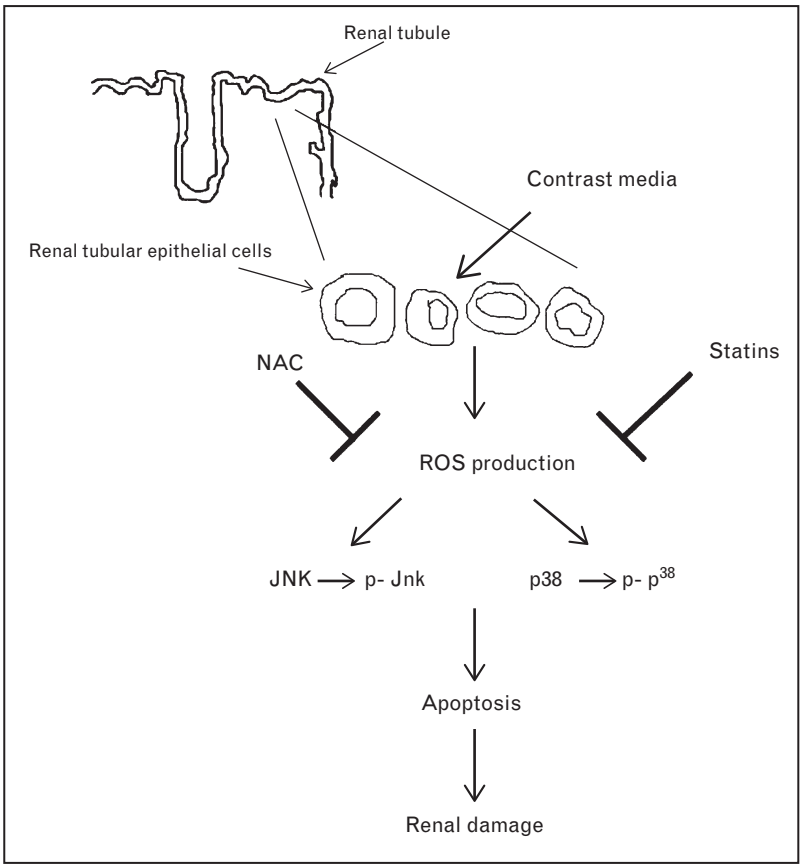

FIGURE 1. Molecular events leading to contrast-induced acute kidney injury. Statins, NAC and other antioxidant compounds act mainly at the renal distal tubules, blocking ROS production. This inhibition results in a decrease of the activation of JNK and p38 stress kinases and thus in a reduction of apoptosis induction that determines renal damage. JNK, c-Jun N-terminal kinase; NAC, n-acetyl cysteine; ROS, reactive oxygen species.

Table 1. RIFLE eAKIN* criteria

RIFLE criteria (7 days)		
Class output	**Criteria: GFR**	**Criteria: urine**
R-Risk 6 h	Increase sCr × 1.5 or GFR decrease >25%	0.5 ml/kg/h
I-Injury for 12 h	Increase sCr × 2 or GFR decrease >25%	<0.5 ml/kg/h
F-Failure 24 h	Increase sCr × 3 or GFR decrease >75%	<0.3 ml/kg/h
12 h	or SCr = 4 mg/cll	or anuria for 12 h
L-Loss	Persistent kidney failure >4 weeks	
E-ESKD	Terminal kidney injury >3 months	

AKIN criteria (48 h)		
Stage output	**Criteria: serum creatinine**	**Criteria: urine**
1 for 6 h	increase of sCr × 1.5 or >0.3 mg/dl	<0.5 ml/kg/hr
2 for 6 h	increase of sCr × 2	<0.5 ml/kg/h
3 for >24 h	increase of sCr × 3 or >4 mg/dl	<0.3 ml/kg/h
		or anuria for 12 h

GFR, glomerular filtration rate; sCr, serum creatinine.

ubiquitous 25-kDa protein (covalently bound to gelatinase from human neutrophils), is a marker of tubular injury [23,24]. Serum NGAL (sNGAL) and urine NGAL (uNGAL) levels have been shown to predict AKI in different clinical settings [25–28], including CI-AKI [29,30]. We have found that NGAL at 6 h after contrast media exposure is a reliable marker for ruling out CI-AKI and predicts 1-year mayor adverse effects (MAE; i.e. death and dialysis, unpublished data). Therefore, detection of elevated sNGAL might enable more rapid conventional interventions or the introduction of novel therapies to prevent or effectively treat such otherwise undetected AKI (Fig. 2) [31].

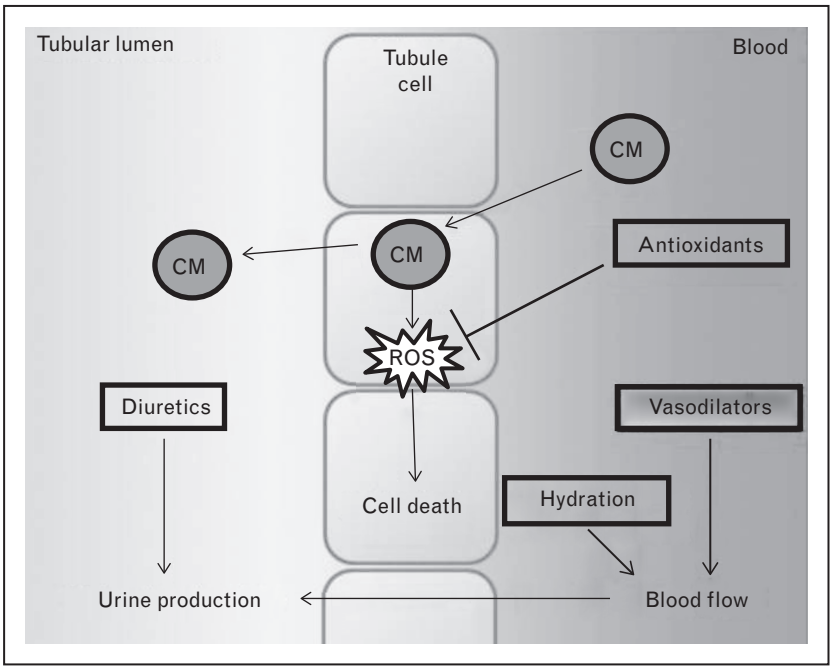

FIGURE 2. Therapeutic approaches to prevent CI-AKI. The approaches currently used to prevent CI-AKI act through different mechanisms. Antioxidant compounds decrease ROS levels, diuretics increase urine production and thus the expulsion of contrast media, and vasodilators and hydration increase blood flow and, thus, urine volume. ROS, reactive oxygen species.

WHO ARE THE PATIENTS AT RISK?

Many studies indicate that major risk factors for CI-AKI are patients with preexisting chronic kidney disease (CKD), diabetes mellitus, high total dose of contrast media, heart failure or other cause of reduced renal perfusion, age and anaemia [17,32,33]. There is a large variability in CI-AKI rate in the literature. This makes it very difficult to estimate the real risk in each single patient and compare different studies or different prophylactic strategies. In general, a clinically relevant renal function deterioration is negligible in patients with normal renal function (even diabetic individuals). Significant AKI is estimated to be 4–11% in patients with mild to moderate renal insufficiency alone (plasma creatinine between 1.5 and 4.0 mg/dl or 132–352 μmol/l) [17,32]. This risk, however, may be increased to more than 40% by more advanced renal dysfunction, marked volume depletion, severe heart failure or multiple contrast studies within a 72-h period. Risk is estimated to be 9–38% in patients with mild to moderate renal insufficiency and diabetes mellitus [34,35]. Risk increases to at least 50% if the baseline plasma creatinine is more than 4 mg/dl (>352 μmol/l), particularly in patients with diabetic nephropathy [32]. In order to help clinicians, some risk scores have been proposed (Table 2) [32,36▪]. The risk score proposed by Mehran *et al.* [32] is calculated according to the following algorithm: hypotension (integer score 5), intra-aortic balloon pump support (integer score 5), congestive heart failure (integer score 4), age more than 75 years (integer score 4), diabetes mellitus (integer score 3), estimated GFR (eGFR) less than 60 (integer score 2–6), preexisting anaemia (integer score 3) and contrast media volume (integer score 1 for each 100 ml). The global scores of 5 or less, 6–10, 11–16 and at least 16 predict a CI-AKI risk of 7.5, 14, 26.1 and 57.3%, respectively. The risk score proposed by Gurm *et al.* [36▪] can be reliably calculated using a novel easy-to-use computational tool (https://bmc2.org/calculators/cin) and differentiate three groups of patients: low risk (<1%), intermediate risk (1–7%) and high risk (>7%). These are very useful in clinical practice for two reasons: first, because they allow a better definition of the risk in each single patient before contrast exposure, and, consequently, they help the clinicians to target the most appropriate prophylactic strategy in each single patient.

STRATEGIES FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY PREVENTION

Multiple lines of evidence suggest that a single intervention strategy may not be successful for CI-AKI prevention. Here, we describe the major strategies developed to prevent CI-AKI.

HYDRATION

Hydration is considered one of the major beneficial measures for CI-AKI prevention [37]. Thus, adequate hydration should be performed before contrast media exposure. Hydration, by inducing an increase of urine flow rates, reduces the concentration of contrast media in the tubule and expedites contrast media excretion. This implies a reduction of the exposure time of tubular cells to the toxic effects of contrast media [38]. A major benefit of hydration is achieved when it is administered intravenously rather than orally [39] and when received for 12 h before and after cardiac catheterization instead of immediately before or during the procedure [40,41]. Limitations of this hydration regimen include preclusion in urgent/emergent settings and suboptimal efficacy in high and very high risk patients. Optimal hydration regimen should be defined according to a predefined clinical marker. Two markers have been identified: urine flow rate [42] and left ventricular end-diastolic pressure (LVEDP) [43▪].

Table 2. Risk scores of contrast-induced acute kidney injury

Mehran *et al.* [32]	Risk	Risk for CI-AKI	Risk of dialysis
Algorithm used			
Global scores <5	Low	<7.5%	0.04%
Global scores 6–10	Intermediate	14%	0.12%
Global scores 11–16	High	26.1%	1.09%
Global scores >16	Very high	57.3%	12.6%
Gurm *et al.* [36▪]			
Algorithm used			
https://bmc2.org/calculators/cin	Low	<1%	<0.10%
	Intermediate	1–7%	0.10–1.5%
	High	>7%	>1.5%

CI-AKI, contrast-induced acute kidney injury.

Urine flow rate

High urine flow rate may reduce the incidence of CI-AKI by several effects. It is important to consider that a high urine flow rate should be reached by maintaining a constant intravascular volume to prevent hypovolemia [42]. Data from the PRINCE study indicate that the increase of the urine flow rate (≥150 ml/h) reduces the toxic effect of contrast media [42]. The RenalGuard system (PLC Medical System, Inc. Franklin, Massachusetts, USA) was developed to facilitate optimal hydration therapy and allows a high urine output while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia [44▪,45,46].

Left ventricular end-diastolic pressure

The POSEIDON trial [43▪] sought to determine the efficacy of a novel fluid protocol based upon the LVEDP. Patients undergoing cardiac catheterization with an estimated GFR of 60 ml/min/1.73 m^2 or less and one or more of diabetes mellitus, history of congestive heart failure, hypertension or age more than 75 years were randomly allocated to LVEDP-guided volume expansion or control group. Both groups received intravenous 0.9% sodium chloride at 3 ml/kg for 1 h prior to cardiac catheterization. In the LVEDP group, the fluid rate was adjusted according to the LVEDP as follows: 5 ml/kg/h for LVEDP less than 13 mmHg; 3 ml/kg/h for 13–18 mmHg; and 1.5 ml/kg/h for more than 18 mmHg. The control group rate was 1.5 ml/kg/h. For both groups, the fluid rate was set at the start of the procedure, continued during the procedure and for 4 h post-procedure. CI-AKI occurred less frequently among patients randomized to the LVEDP-guided group than the control group (6.7 vs. 16.3%, $P = 0.005$).

WHICH INTRAVENOUS FLUID?

It is still controversial whether some fluids are superior to others (namely, sodium bicarbonate vs. sodium chloride). Sodium bicarbonate improves urine alkalization and probably decreases the concentration of contrast media in the renal tubules [47]. Two meta-analyses did not identify a benefit of sodium bicarbonate vs. sodium chloride in preventing CI-AKI [48]. In addition, the recent Bicarbonate or Saline Study (BOSS) also failed to demonstrate a benefit of sodium bicarbonate over sodium chloride solution in preventing CI-AKI, although the death rate was lower in the group that received sodium bicarbonate [49].

ANTIOXIDANT COMPOUNDS

As contrast media exposure of vasa recta and tubule cells cause an increase of ROS production and, consequently, apoptosis activation, compounds with antioxidant proprieties acting as scavenger molecules for ROS [such as N-acetyl cysteine (NAC) and statins] have been investigated.

N-ACETYLCYSTEINE

NAC is a thiol compound classically known as a mucolytic agent, which is used to thin mucus in patients with respiratory disorders. NAC is a potent antioxidant that scavenges a wide variety of oxygen-derived free radicals and may be capable of preventing AKI [50–52]. The results on the use of NAC are conflicting. Initial studies by Tepel *et al.* [53] showed that NAC (600 mg orally twice daily) and hydration (with normal saline) before and after administration of contrast media was more effective than hydration alone in preventing CI-AKI in patients with CKD undergoing computed tomography. However, a recent large randomized trial [54] failed to demonstrate the superiority of NAC vs. placebo in reducing the incidence of CI-AKI in patients undergoing coronary angiography study. A recent meta-analysis of 30 trials did demonstrate a renoprotective benefit of NAC [55]. Even if the clinical data are controversial, the molecular mechanisms of NAC on CI-AKI prevention have been clearly elucidated in in-vitro experiments. Our studies demonstrate that NAC exerts its antioxidant properties preventing kidney cell death by inhibiting oxygen free radical production and thus stress kinases and apoptosis activation upon contrast media exposure [2,8,15,56,57]. The protective role of NAC on kidney cells has also been reported in noncontrast media agent induced kidney injury. Thus, larger clinical studies and trials are required to elucidate their potential effect on CI-AKI prevention.

STATINS

Apart from the main use of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) to control cholesterol levels, they have several 'pleiotropic' effects through their nonlipid-related mechanisms. They modulate inflammatory responses, endothelial function, plaque stability, thrombus formation and apoptosis [58]. Several studies have investigated the effectiveness of statins pretreatment in reducing the incidence of CI-AKI [59–63]. Our study demonstrated that a single high (80 mg) loading dose of atorvastatin administered within 24 h of contrast media exposure is effective in reducing the rate of CI-AKI in patients with CKD [15]. Furthermore, our in-vitro model indicates that the pretreatment with atorvastatin prevents contrast media induced renal cell apoptosis by reducing

stress kinases activation and restored the survival signals mediated by Akt and Erks signal transduction pathways [15]. Moreover, recent investigations also confirmed that rosuvastatin in statin-naive patients with both stable and acute coronary syndrome scheduled for early invasive procedure can prevent CI-AKI [63].

VASODILATOR COMPOUNDS

Several vasodilator drugs have been tested for prevention of CI-AKI, but have not shown any benefit (theophylline [64], nifedipine [65], adenosine [66], endothelin receptor antagonists [67], atrial natriuretic peptide [68], dopamine [69–71]). A randomized, double-blind, placebo-controlled trial showed that prophylactic administration of iloprost (inhaled prostaglandin I2 analogue approved for the treatment of pulmonary hypertension) in patients with CKD, undergoing coronary angiography and/or intervention, may protect against CI-AKI [72].

DIURETICS

Compelling data support that neither mannitol nor furosemide offers additional protection against CI-AKI as compared with saline hydration alone in either diabetic or nondiabetic patients. In the study by Solomon and Deray [16], there were no beneficial effects of the osmotic diuretic mannitol when added to saline hydration in either diabetic or nondiabetic patients, and there was an actual exacerbation of CI-AKI with the use of the loop diuretic furosemide with saline hydration. In a small study of 18 patients, furosemide pretreatment (1.5 mg/kg) added to an intravenous fluid protocol was associated with significantly worse renal function than intravenous fluid alone [73]. Significant weight loss was observed in the patients treated with furosemide, suggesting that the potentially deleterious effect of furosemide was the result of a negative fluid balance. Theoretically, furosemide should protect the kidney by reducing the outer medullary hypoxia caused by contrast media by blocking the Na-K-2Cl transporter in the medullary thick ascending limb [74]. This approach, however, has actually been shown to be deleterious and to increase the rates of CI-AKI [75]. It has been suggested that the deleterious effect observed is a result of a negative fluid balance [73,75].

RENAL REPLACEMENT THERAPY

Some data suggest the potential role of hemofiltration for the prevention of CI-AKI in high-risk patients [76]. Concerns, however, have been raised following this study, including that the creatinine removal by the hemofiltration procedure may explain the decreased frequency of elevation in the serum creatinine, their greater intensity of care relative to the control group may explain why hemofiltration was associated with improved short and long-term survival, and that hemofiltration is expensive, logistically cumbersome and associated with significant risks.

REMOTE ISCHEMIC PRECONDITIONING

In addition to the effects of local ischemia, remote ischemia can protect distant organs or tissue during subsequent ischemia [77]. This has been termed remote ischemic preconditioning (RIPC) [78]. RIPC is a method by which the deliberate induction of transient nonlethal ischemia of an organ protects against subsequent ischemic injury of another organ. The potential use of RIPC has been mostly evaluated in the setting of myocardial protection. There are, also, preliminary data suggesting that RIPC prior to both cardiac surgery and contrast media administration protects against AKI [79]. In one randomized, double-blind trial, 100 patients with CKD were subjected to RIPC or to a sham procedure prior to elective coronary angiography [80]. RIPC was induced by intermittent arm ischemia generated by four cycles of 5-min inflation of a blood pressure (BP) cuff to 50 mmHg above individual systolic pressure within 45 min before angiography. The sham procedure consisted of inflation of a BP cuff to individual diastolic pressure, followed by deflation to 10 mmHg. All patients also received acetylcysteine and a continuous physiological saline infusion. The incidence of CI-AKI was 6% in the RIPC group vs. 20% in the sham group [odds ratio (OR) 0.21, 95% confidence interval (95% CI) 0.07–0.57]. In a second trial, 225 patients with a non-ST segment elevation myocardial infarction were randomly assigned to receive RIPC or a sham procedure prior to the coronary intervention [81]. RIPC consisted of four cycles of 30-s inflation, followed by 30 s deflation of the stent balloon during the PCI procedure; the sham procedure consisted of four cycles of 30-s inflation to only 3 atm pressure, followed by deflation. Even in this study, CI-AKI occurred less frequently in the RIPC group than in the sham group (12.4 vs. 29.5%, respectively, OR 0.34, 95% CI 0.16–0.71). These results, although compelling (particularly because RIPC is conferred using different modalities and at different time points prior to contrast exposure), require confirmation in larger randomized trials and before RIPC can be recommended as a preventive measure for

Table 3. Checklist for the assessment of the risks for contrast-induced acute kidney injury and prophylactic strategies in patients scheduled for diagnostic or interventional coronary procedures

Risk assessment		
eGFR calculation	High risk: <60 ml/min/l.73 m^2	
Risk score assessment	See ref. [14] and Gurm *et al.* [36▪]	
Nephrologic conciliation (eGFR <15 ml/min/1.73 m^2)	Indication for elective RRT	
Prophylaxis		
Intravenous hydration	Normal saline	0.5–1 ml/kg/h 12 h before and 12 h after Maintain urine flow rate >150 ml/h Or LVEDP-guided: <13 mmHg = 5 ml/kg/h 13–18 mmHg = 3 ml/kg/h >18 mmHg = 1.5 ml/kg/h
	Sodium bicarbonate	154 mEq/l (3 ml/kg/h = 1 h before and 1 ml/kg/h 6 h after)
	Renal guard system (eGFR <30 Maintain urine flow rate = 300 ml/min/1.73 m^2 or risk score >11 ml/h)	
Drugs	Statin	Atorvastatin 80 mg Rosuvastatin 40 mg
	N-acetyl-cysteine	1200 mg b.i.d. before and after
Iodinated contrast media	Iso-molar and low-osmolar (apart from ioxalatc and ioexol)	
	Limited volume (ml)	Max volume = 5 × crea/kg Prolong the time-interval between CM-enhanced studies Alternative CM (CO_2 for peripheral procedures; gadolinium is contraindicated)
Serial control of scrum creatinine	At 48–72 h. Additional controls if clinically indicated	

b.i.d., twice daily; CM, contrast media; eGFR, estimated glomerular filtration rate; LVEDP, left ventricular end-diastolic pressure; RRT, renal replacement therapy.

CI-AKI [57]. In addition, the safety of repetitive balloon inflations in a coronary artery poststenting remains unclear.

CONCLUSION

AKI may occur following contrast media exposure, especially in patients with risk factors, including older age, CKD, congestive heart failure and diabetes mellitus. The administration of a limited volume of contrast media and adequate hydration (either by saline or sodium bicarbonate infusion) may prevent CI-AKI. Adequate hydration should be guided according to the urine flow rate and in those patients undergoing coronary angiography perhaps by LVEDP-guided fluid replacement. A high dose of statins (atorvastatin or rosuvastatin, or both) may be effective, probably by reducing oxidative stress and therefore preventing renal cell apoptosis. Although the effectiveness of NAC in preventing CI-AKI is still controversial, its antioxidant and antiapoptotic properties may have a clinically appreciable effect in high-risk patients. Despite these strategies, however, CI-AKI may still occur in patients at a high risk. The preliminary and promising results of RIPC require confirmation in larger randomized trials before this strategy can be recommended for CI-AKI prevention. The discovery of novel and reliable markers of CI-AKI may allow early therapeutic interventions and, potentially, a more favourable outcome. In Table 3, we summarize our approach to prevent CI-AKI.

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Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Chertow GM, Burdick E, Honour M, *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16:3365–3370.
2. Brown JR, Thompson CA. Contrast-induced acute kidney injury: the at-risk patient and protective measures. Curr Cardiol Rep 2010; 12:440–445.
3. Schwab SJ, Hlatky MA, Pieper KS, *et al.* Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med 1989; 320:149–153.
4. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993; 188:171–178.
5. Steinberg EP, Moore RD, Powe NR, *et al.* Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. N Engl J Med 1992; 328:425–430.
6. Kay J, Chow WH, Chan TM, *et al.* Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003; 289:553–558.
7. Heinrich MC, Kuhlmann MK, Grgic A, *et al.* Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells *in vitro*. Radiology 2005; 253:843–849.
8. Romano G, Briguori C, Quintavalle C, *et al.* Contrast agents and renal cell apoptosis. Eur Hearth J 2008; 29:2569–2576.
9. Andersen KJ, Christensen EI, Vik H. Effects of iodinated x-ray contrast media on renal epithelial cells in culture. Invest Radiol 1994; 29:955–962.
10. Zager RA, Johnson AC, Hanson SY. Radiographic contrast media-induced tubular injury: evaluation of oxidant stress and plasma membrane integrity. Kidney Int 2003; 64:128–139.
11. Hizoh I, Strater J, Schick CS, *et al.* Radiocontrast-induced DNA fragmentation of renal tubular cells *in vitro*: role of hypertonicity. Nephrol Dial Transplant 1998; 13:911–918.
12. Katholi RE, Woods WTJ, Taylor GJ, *et al.* Oxygen free radicals and contrast nephropathy. Am J Kidney Dis 1998; 32:64–71.
13. Drager LF, Andrade L, Barros de Toledo JF, *et al.* Renal effects of N-acetylcysteine in patients at risk for contrast nephropathy: decrease in oxidant stress-mediated renal tubular injury. Nephrol Dial Transplant 2004; 19:1803–1807.
14. Quintavalle C, Brenca M, De Micco F, *et al. In vivo* and *in vitro* assessment of pathways involved in contrast media-induced renal cells apoptosis. Cell Death Dis 2011; 2:e155.
15. Quintavalle C, Fiore D, De Micco F, *et al.* Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012; 126:3008–3016.
16. Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. Kidney Int Suppl 2006; 100:S51–S53.
17. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2008; 51:1419–1428.
18. Solomon R, Barrett B. Follow-up of patients with contrast-induced nephropathy. Kidney Int Suppl 2006; 100:S46–S50.
19. Harjai KJ, Raizada A, Shenoy C, *et al.* A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. Am J Cardiol 2008; 101:812–819.
20. Hatano M. Clinical study of tubular creatinine secretion in renal dysfunction. Nippon Jinzo Gakkai Shi 1991; 33:1097–1104.
21. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002; 40:221–226.
22. Herget-Rosenthal S, Marggraf G, Husing J, *et al.* Early detection of acute renal failure by serum cystatin C. Kidney Int 2004; 66:1115–1122.
23. Cowland JB, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 1997; 45:17–23.
24. Mishra J, Ma Q, Prada A, *et al.* Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14:2534–2543.
25. Mishra J, Dent C, Tarabishi R, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365:1231–1238.
26. Wheeler DS, Devarajan P, Ma Q, *et al.* Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Crit Care Med 2008; 36:1297–1303.
27. Zappitelli M, Washburn KK, Arikan AA, *et al.* Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care 2007; 11:R84.
28. Wagener G, Gubitosa G, Wang S, *et al.* Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008; 52:425–433.
29. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, *et al.* Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. Am J Nephrol 2006; 26:287–292.
30. Hirsch R, Dent C, Pfriem H, *et al.* NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol 2007; 22:2089–2095.
31. Ronco C, Haapio M, House AA, *et al.* Cardiorenal syndrome. J Am Coll Cardiol 2008; 52:1527–1539.
32. Mehran R, Aymong ED, Nikolsky E, *et al.* A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44:1393–1399.
33. Parfrey PS, Griffiths SM, Barrett BJ, *et al.* Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. N Engl J Med 1989; 320:143–149.
34. Manske CL, Sprafka JM, Strony JT, *et al.* Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990; 89:615–620.
35. Aspelin P, Aubry P, Fransson SG, *et al.* Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348:491.
36. ■ Gurm HS, Seth M, Kooiman J, *et al.* A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2013; 61:2242–2248.

This study describes an accurate and easy algorithm for the calculation of risk of CI-AKI. It is very useful for clinical decisions in the treatment of high-risk patients.

37. Stacul F, van der Molen AJ, Reimer P, *et al.* Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2011; 21:2527–2541.
38. Seeliger E, Becker K, Ladwig M, *et al.* Up to 50-fold increase in urine viscosity with iso-osmolar contrast media in the rat. Radiology 2010; 256:406–414.
39. Trivedi HS, Moore H, Nasr S, *et al.* A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 2003; 93:C29–C34.
40. Bader BD, Berger ED, Heede MB, *et al.* What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? Clin Nephrol 2004; 62:1–7.
41. Krasuski RA, Beard BM, Geoghagan JD, *et al.* Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. J Invasive Cardiol 2003; 15:699–702.
42. Stevens MA, McCullough PA, Tobin KJ, *et al.* A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C. E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J Am Coll Cardiol 1999; 33:403–411.
43. ■ Briguori C, Condorelli G. Hydration in contrast-induced acute kidney injury. Lancet 2014; 383:1786–1788.

This article discusses the role of hydration in CI-AKI.

44. ■ Dorval J-F, Dixon SR, Zelman RB, *et al.* Feasibility study of the RenalGuard balanced hydration system: a novel strategy for the prevention of contrast-induced nephropathy in high risk patients. Int J Cardiol 2013; 166:482–486.

This article confirms that the renal guard protocol is well balanced and hydrodynamic balanced, but further investigation is needed for the assessment of its impact on CI-AKI prevention.

45. Briguori C, Visconti G, Focaccio A, *et al.* Renal insufficiency after contrast media administration trial II (REMEDIAL II) /clinical perspective. Circulation 2011; 124:1260–1269.
46. Briguori C, Visconti G, Ricciardelli B, *et al.* Renal insufficiency following contrast media administration trial II (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury: rationale and design. EuroIntervention 2011; 6:1117–1122.
47. Briguori C, Airoldi F, D'Andrea D, *et al.* Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation 2007; 115:1211–1217.
48. Brar SS, Hiremath S, Dangas G, *et al.* Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2009; 4:1584–1592.
49. Solomon R. Randomized trial for the prevention of contrast induced nephropathy in patients with chronic kidney disease: the Bicarbonate or Saline Study (BOSS). TCT 2013 meeting; 28 October 2013; San Francisco, CA.
50. DiMari J, Megyesi J, Udvarhelyi N, *et al.* N-acetyl cysteine ameliorates ischemic renal failure. Am J Physiol 1997; 272:F292–F298.
51. Heyman SN, Goldfarb M, Shina A, *et al.* N-acetylcysteine ameliorates renal microcirculation: studies in rats. Kidney Int 2003; 63:634–641.
52. Tariq M, Morais C, Sobki S, *et al.* N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant 1999; 14:923–929.

53. Tepel M, van der Giet M, Schwarzfeld C, *et al.* Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000; 343:180–184.

54. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT). Circulation 2011; 124:1250–1259.

55. Kelly AM, Dwamena B, Cronin P, *et al.* Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008; 148:284–294.

56. Briguori C, Quintavalle C, De Micco F, *et al.* Nephrotoxicity of contrast media and protective effects of acetylcysteine. Arch Toxicol 2011; 85:165–173.

57. Bonventre JV. Limb ischemia protects against contrast-induced nephropathy. Circulation 2012; 126:384–387.

58. Lev EI, Kornowski R, Vaknin-Assa H, *et al.* Effect of previous treatment with statins on outcome of patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2009; 103:165–169.

59. Jo S-H, Koo B-K, Park J-S, *et al.* Prevention of radiocontrast medium induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial a randomized controlled study. Am Heart J 2008; 155:499.e1–499.e8.

60. Toso A, Maioli M, Leoncini M, *et al.* Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. Am J Cardiol 2010; 105:288–292.

61. Patti G, Ricottini E, Nusca A, *et al.* Short-term, high-dose atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [Atorvastatin for Reduction of MYocardial Damage during Angioplasty–Contrast-Induced Nephropathy] trial. Am J Cardiol 2011; 108:1–7.

62. Xinwei J, Xianghua F, Jing Z, *et al.* Comparison of usefulness of simvastatin 20 mg versus 80 mg in preventing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol 2009; 104:519–524.

63. Toso A, Leoncini M, Maioli M, *et al.* Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome. J Am Coll Cardiol 2014; 63:71–79.

64. Katholi RE, Taylor GJ, McCann WP, *et al.* Nephrotoxicity from contrast media: attenuation with theophylline. Radiology 1995; 195:17–22.

65. Bakris GL, Burnett JC Jr. A role for calcium in radiocontrast-induced reductions in renal hemodynamics. Kidney Int 1985; 27:465–468.

66. Pflueger A, Larson TS, Nath KA, *et al.* Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. Mayo Clin Proc 2000; 75:1275–1283.

67. Wang A, Holcslaw T, Bashore TM, *et al.* Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int 2000; 57:1675–1680.

68. Kurnik BR, Allgren RL, Genter FC, *et al.* Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998; 31:674–680.

69. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. Kidney Int 1999; 56:206–210.

70. Stone GW, McCullough P, Tumlin J, *et al.* A prospective, randomized placebo-controlled multicenter trial evaluating fenoldopam mesylate for the prevention of contrast induced nephropathy: the CONTRAST trial. J Am Coll Cardiol 2003; 41:83–84.

71. Briguori C, Colombo A, Airoldi F, *et al.* N-Acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. J Am Coll Cardiol 2004; 44:762–765.

72. Spargias K, Adreanides E, Demerouti E, *et al.* Iloprost prevents contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2009; 120:1793–1799.

73. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron 1992; 62:413–415.

74. Liss P, Nygren A, Ulfendahl HR, *et al.* Effect of furosemide or mannitol before injection of a nonionic contrast medium on intrarenal oxygen tension. Adv Exp Med Biol 1999; 471:353–359.

75. Solomon R, Werner C, Mann D, *et al.* Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331:1416–1420.

76. Marenzi G, Marana I, Lauri G, *et al.* The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003; 349:1333–1340.

77. Przyklenk K, Bauer B, Ovize M, *et al.* Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 1993; 87:893–899.

78. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. Cardiovasc Res 2008; 79:377–386.

79. Igarashi G, Iino K, Watanabe H, *et al.* Remote ischemic preconditioning alleviates contrast-induced acute kidney injury in patients with moderate chronic kidney disease. Circ J 2013; 77:3037–3044.

80. Er F, Nia AM, Dopp H, *et al.* Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). Circulation 2012; 126:296–303.

81. Deftereos S, Giannopoulos G, Tzalamouras V, *et al.* Renoprotective effect of remote ischemic postconditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2013; 61:1949–1955.