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Original article

Cardiological Society of India Practice Guidelines for Angiography in Patients with Renal Dysfunction

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Preamble: The potential risk of contrast-induced acute kidney injury (CI-AKI) has made utilization of coronary angiography in the work-up for the diagnosis of coronary artery disease in CKD quite low.[1] This is in contrast to increasing prevalence and severity of CAD as the serum creatinine rises.[2] In fact most CKD patients will succumb to CAD and not to ESRD.[3] Thus the judicious use of CAG/PCI in this setting is of prime importance but underused.

The CSI began to develop guidelines for Indian context as most guidelines are those developed by ACC/AHA or ESC. The aim was to assist the physicians in selecting the best management strategy for an individual patient under his care based on an expert committee who would review the current data and write the guidelines with relevance to the Indian context.

The guidelines were developed initially in June 2010 as an initiative of Delhi CSI. Three interventional cardiologist (SB, AS, KKS), one nephrologist (SCT) and two clinical cardiologists (ST, RG) along with Dr. Roxana Mehran (New York) and Dr. Peter McCullough (Missouri), U.S.A.; were involved in a three-way teleconference to discuss/debate the data. This was presented by SB, and over the next two hours each data subset was debated/

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agreed/deleted and this resulted in the "Guidelines for CAG in Renal Dysfunction Patients". These were then written and re- circulated to all for final comments.

Further, these guidelines were updated and additional Task Force Members nominated by Central CSI were involved in the formation of the final CSI Guidelines. Both (Roxana Mehran and Peter McCullough) reviewed these updated Guidelines in October 2012 and after incorporating the views of all the Task Force members—the final format is as it is presented in this final document.

Thus the following document details the existing literature on contrast induced acute kidney injury (CI-AKI) and offers a class I–III indications approach, as yet undescribed in the world literature.

Guidelines for contrast induced nephropathy (CI-AKI)

1. *Angiography in patients with renal dysfunction*

Advancing age and the epidemic of diabetes the worldover have contributed to increasing number of patients with renal dysfunction who need angiography or coronary interventions. Iodinated contrasts, which are essential for an angiogram or PTCA, are also toxic to the kidneys causing up to 10% of hospital acquired renal insufficiency.[4]

2. *Definition of CI-AKI*

CI-AKI is defined as an impairment of renal functions subsequent to the administration of contrast media (CM) in the absence of any other cause. In most trials CI-AKI is defined as absolute increase of the serum creatinine concentration of 0.5 mg/dl or a relative increase of 25% from the baseline within 72 hours of CM administration.[5] The recovery occurs in majority of cases within 2–3 weeks, few patients require dialysis for recovery.[6]

3. *Incidence of CI-AKI*

Owing to better awareness of CI-AKI; its incidence has sharply declined in the last decade from 15% to 7%.[7] In the overall general population the incidence is low to 2%, but in the high-risk groups (CHF, anemia, elderly, diabetics and preceding CKD), the incidence of CI-AKI has been calculated to be 20–30%.[8–13] In one study CI-AKI occurred in 2%, 10.4% and 62% of the patients with baseline S. creatinine levels of <1.2 mg/dl; 1.3–1.9 mg/dl; and >2.0 mg/dl, respectively.[14] Risk of CI-AKI is important when baseline S. creatinine is ≥1.3 mg/dl is men and >1.0 mg/dl in female (equivalent eGFR < 60 ml/min/1.73 m^2). The need for dialysis after CI-AKI, varies according to patients underlying risks at the time of contrast administration, but is generally <1%[15] but may increase to 3% in patients with underlying renal impariment[16] and in patients undergoing primary PCI for MI.[17]

Contrast-induced AKI has serious prognostic implications. It is linked to increase in length of hospital stay and higher rates of in-hospital cardiovascular events, in-hospital mortality, and 1-year and 5-year mortality rates (Figure 1). The risk of death during hospitalization of around 34% in patients with CI-AKI vs 7% without CI-AKI, attests to the need to prevent this catastrophic effect of angiography.[18]

4. *PATHOPHYSIOLOGY OF CI-AKI*

A. Renal Ischemia

After contrast is injected, renal blood flow transiently increases and then decreases over a longer time, suggesting that renal ischemia is a major factor in the pathogenesis of CI-AKI (Figure 2).[19]

In experimental studies of CI-AKI, the kidneys show pathologic ischemic changes—necrosis of the medullary thick ascending limbs as well as tubular collapse and casts-primarily in the outer medullary area of the kidney.[20] Moreover, contrast agents cause a marked decrease in medullary oxygenation that can be directly measured with oxygen microelectrodes.[21]

Based on these observations, the following mechanism for acute renal failure induced by contrast agents has been proposed.[22,23]

Even under normal conditions, the renal medulla is poorly oxygenated, making it particularly susceptible to hypoxic injury. The oxygen tension in the medulla is 10–20 mm hg compared with 50 mmHg in the cortex. Reasons for the low oxygen tension are countercurrent exchange of oxygen between the vasa recta and oxygen use by active transport of sodium in the ascending limb of the loop of Henle.[22]

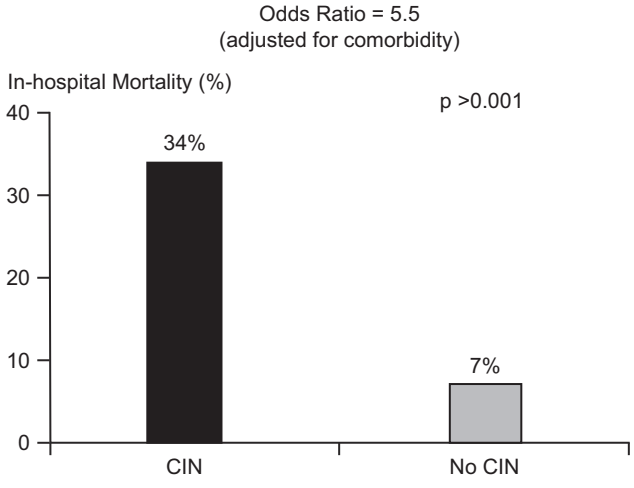


Fig. 1 – Hospital mortality is higher in patients with (CI-AKI). (Adapted from *JAMA*[16]).

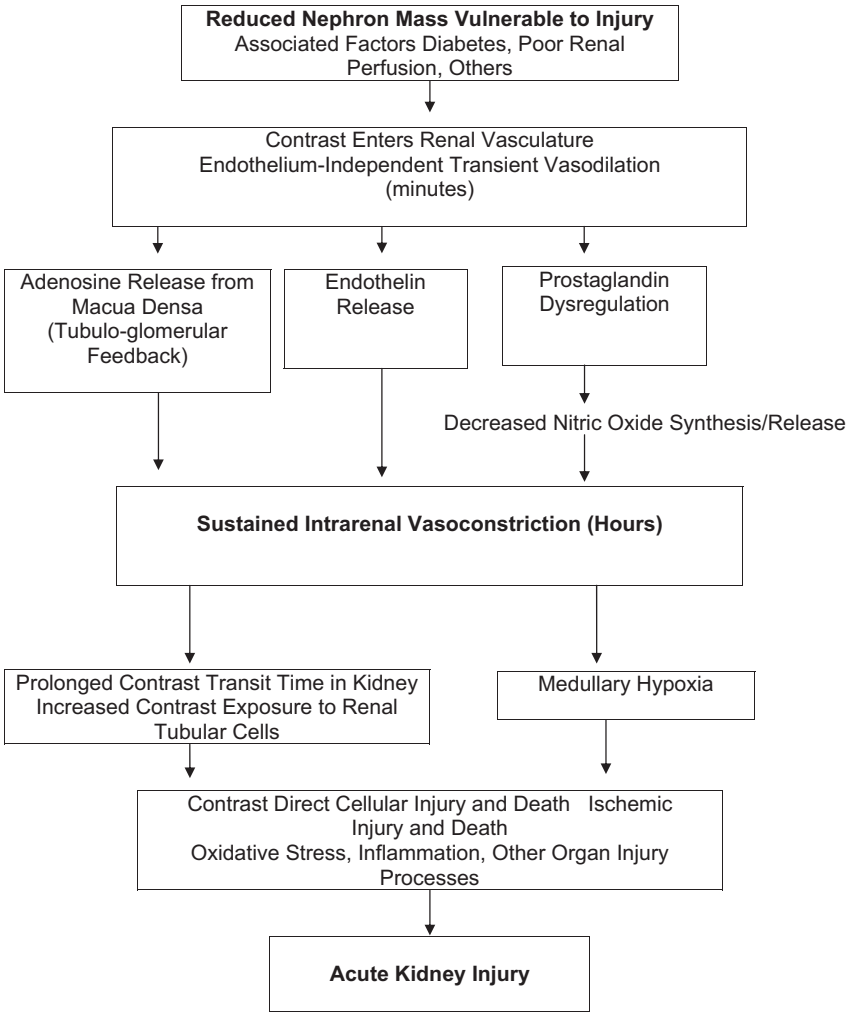


Figure 2 – Pathophysiologic mechanisms of CI-AKI.

Contrast agents reduce the oxygen tension in both the cortex and the medulla.[21] This effect may be due to increased work of active transport in response to an osmotic diuresis from hyperosmolar agents, as well as the release of vasoconstrictive compounds such as endothelin. Furthermore, blockade of vasodilatory compounds such as nitrous oxide and prostaglandins appears to markedly exacerbate contrast induced medullary hypoxic injury.[22]

B. Vasoconstriction

Many substances may mediate renal vasoconstriction and subsequent hypoxic injury. Of note, adrenergic stimulation and activation of the renin-angiotensin system do not seem to be involved in contrast induced vasoconstriction.[19,20] Prostaglandins with vasodilatory properties may counter the vasoconstriction induced by contrast media, since pretreatment with indomethacin is necessary to induce experimental contrast induced renal injury.[21]

C. Endothelin

Multiple experimental observations suggest that endothelin, a potent renal vasoconstrictor, may play a critical role in contrast mediated vasoconstriction.[24]

These observations led to a clinical trial in which patients with chronic kidney disease undergoing cardiac angiography were randomized to receive either the endothelin receptor antagonist SB290670 or placebo.[25] Surprisingly, the incidence of CI-AKI was higher in the treatment group (56%) than in the placebo group (29%; $P = 0.002$).

D. Adenosine

The role of adenosine in the pathogenesis of CI-AKI is described in detail in an excellent review by Pflueger et al.[26] Adenosine causes vasodilatation through A2 stimulation of the efferent arteriole and medullary capillaries, and it also causes vasoconstriction through A1 stimulation of the afferent arterioles. However, renal vasoconstriction dominates, explaining why intrarenal adenosine infusion results in a decrease in renal blood flow.[26]

In experimental studies, theophylline, a nonselective adenosine receptor antagonist, inhibited contrast media induced renal vasoconstriction.[26]

E. Role of Osmolatity

Several clinical and experimental observations suggest that the hyperosmolality of contrast media may play a role in the

pathogenesis of CI-AKI. Clinical studies demonstrated that low osmolar contrast agents cause less nephrotoxicity than high osmolar agents.[27,28] Furthermore, in one study,[29] the incidence of CI-AKI was lower with an iso-osmolar contrast agent than with a low-osmolar agent.

In experimental studies, hypertonic solutions of saline or mannitol reduce the glomerular filtration rate and renal blood flow and increase enzymuria similarly to high osmolar contrast media but with a lesser magnitude.[19,30] A theory to account for these nonspecific adverse effects is that hyperosmolality activates tubuloglomerular feedback or causes an increase in tubular hydrostatic pressures, either of which could lead to a decrease in glomerular filtration. In addition, the osmotic diuresis produced by contrast media may result in increased active transport of sodium in the thick ascending limb and also in vasoconstriction, and both of these could lead to worsened medullary hypoxemia.[21–23]

On the other hand, most studies in animals specifically comparing iso-osmolar contrast agents (iodixanol and iotrolan) with high osmolar and low osmolar contrast agents have not demonstrated any lower rate of renal abnormalities with the iso-osmolar agents.[31,32]

The reason may be that the iso-osmolar are more viscous, which could increase red blood cell aggregation and decrease renal blood flow, offsetting any reduction in medullary hypoxemia from their lower osmolality.

F. Reactive oxygen species

Reactive oxygen species formed as a result of post-ischemic oxidative stress can lead to acute renal failure through their direct effects on renal endothelial cells, which include apoptotic cell death. Adenosine's role in the pathogenesis of CI-AKI may be due to this molecule's ability to increase generation of oxygen free radicals.[33] The possible benefit of N-acetylcysteine and sodium bicarbonate in preventing CI-AKI is hypothesized to be due to the ability of these compounds to mitigate oxidative injury.

G. Direct cellular toxicity

A number of experimental observations suggest that contrast agents are directly toxic to kidneys cells, causing proximal cell vacuolization, interstitial inflammation, cellular necrosis, and enzymuria.[24,20] Furthermore, suspensions of proximal tubular segments exposed to contrast media showed abnormalities in several markers of cellular injury, that were potentiated by hypoxia and were more pronounced with high-osmolar agents than with low-osmolar agents.[34]

5. *Proposed Scheme for guidelines for RDA (renal dysfunction angiography)*

The proposed guidelines for RDA are based on the ACC/EH class I–III indications and are as detailed below:

Class I: Evidence for and/or general agreement that the procedure or treatment is beneficial, useful, effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about usefulness/efficacy of procedure or treatment.

Class IIa: Weight of evidence/opinion is in form of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Level of evidence

A: Multiple RCTs favor it

B: Single randomized trial/non-randomized trials favor it

C: Consensus of experts, Case studies, standard of care favor this.

6 A: Assessment of risk for CI-AKI prior to angiography in RDA (screening)

Class I:

1) Use e-GFR instead of S. creatinine alone. (Level of Evidence C)

2) Use of risk score (e.g. Mehran et al) (Level of Evidence B)

Multiple CI-AKI risk factors in the same patient or high risk scenario create a high risk (50%) for CI-AKI and (15%) ARF requiring dialysis after contrast exposure.

3) Nephrology consult for eGFR $\leq$ 30 ml/min (Level of Evidence C)

4) Admit 12 hours prior for eGFR $\leq$ 30 ml/min for hydration and continue it post procedure. (Level of Evidence C)

It is well established that abnormal baseline S creatinine, low eGFR and CKD are the most important risk factors for CI-AKI (Figure 3–4).

6A (i) Estimation of GFR

It is best determined by measuring renal excretion of a suitable marker such as inulin that is freely filtered at the glomerulus and not reabsorbed or secreted in the tubule.

Practically, GFR is measured by MDRD[35] (modification of diet in renal disease) or Cockcroft-Gault[36] formula.

Serum creatinine is a rough estimate of renal function. This is so because levels of serum creatinine is determined not only by excretion (which is determined by kidneys) but also by

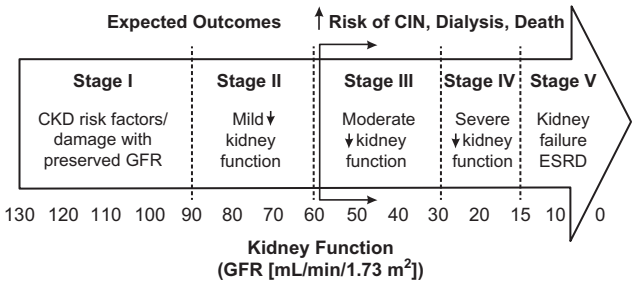


Fig. 3 – shows the stages of CKD based on the level of kidney functions.

its formation (which depends on multiple risk factors such as diet, muscle mass and sex).[37,38] So an elderly person with a poor muscle mass may have S. creatinine within normal range despite having severe reduction in GFR.[35]

Moreover since the relation between serum creatinine and GFR is non-linear, substantial reduction in GFR may occur before serum creatinine is significantly raised.[39]

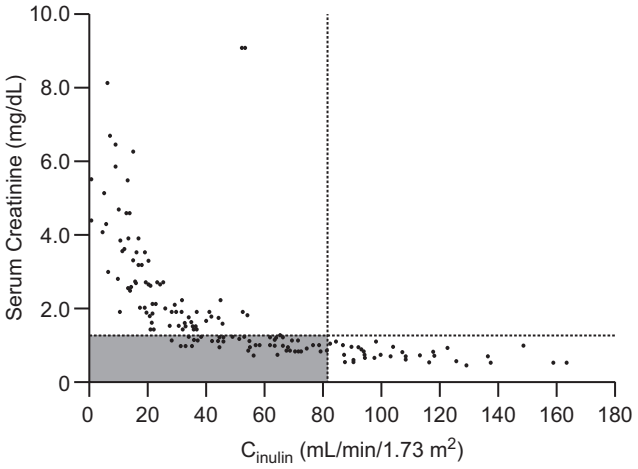


Fig. 4 – Relation between serum creatinine and glomerular filtration rate (GFR). The shaded area includes values for patients in whom GFR is reduced but serum creatinine concentration remains normal. Cinulin _ inulin clearance. (Reprinted from *Am J Kidney Dis*.[39] Copyright 2002, with permission from the National Kidney Foundation)

Hence eGFR (estimated glomerular filtration rate) rather than serum creatinine should be the index of renal function.

National kidney foundation kidney disease outcome quality initiative (k/DOQI) recommends eGFR and that laboratories should provide the clinician with it.[39]

Cockcroft-Gault formula. It determines creatinine clearance rather than GFR.

$$\text{Creatinine clearance(ml/min)} = \frac{(140 - \text{age}) \times \text{weight(kg)} \times 1.23}{\text{Serum creatinine}(\mu\text{mol/L})}$$

Multiply by 0.85 for women
1mg/dl = 88.4μmol/L

K/DOQI recommends abbreviated MDRD for eGFR[39] as Cockcroft-Gault formula is not corrected for body surface area.

Modified MDRD equation.

$$\text{GFR(ml/min/1.73m}^2) = 186 \times \text{serum creatinine}^{-1.154}\ (\mu\text{mol/L}) \times \text{age}^{-0.203}$$
$$(\times\ 0.742 \text{ if patient is a women})$$
$$(\times\ 1.21 \text{ if the patient is black})$$

Review of literature supports the use of the modified MDRD equation as a better estimate of eGFR in patients with moderate to severe renal insufficiency.[40]

The CI-AKI consensus working panel unanimously supported the use of eGFR, calculated from the serum creatinine level using the modified MDRD equation, as the best indicator of renal function (Table 1–2).

All these statement and formulae apply for patients with stable renal function. In hemodynamically unstable and critically-ill patients such as shock, CHF, sepsis, ventilator patients—the risk is much greater.

Serum creatinine levels. Risk of CI-AKI becomes important when serum creatinine level is ≥1.3 mg/dl in men and ≥1 mg/dl in women, equivalent to an eGFR of < 60 ml/min/1.73 m^2.

In a study of 1,144 patients undergoing diagnostic cardiac catheterization, the risk of CI-AKI was low and constant till serum creatinine <1.2 mg/dl.[41] Above this level, risk of CI-AKI increased with serum creatinine level.

So it is important to assess renal function before administration of contrast medium to ensure that appropriate steps are taken to minimize the risk.

Risk factor survey/questionnaires:. When serum creatinine values are not available a simple survey or questionnaire may be used for prediction of patients with higher risk of CI-AKI.

Number of questionnaire have been formulated with a high negative predictive value (97–99%) (Tables 3–5).

Majority of patients with CKD would have one or more positive responses.

For elective catheterization procedures, serum creatinine value should be available.

Emergency situations. If the benefit of immediate angiography outweighs the risk of waiting for serum creatinine result such as patients with acute MI, ACS with cardiogenic shock, one may proceed without the results of serum creatinine or GFR estimation.

But one may still consider the need to identify at risk patients (by a questionnaire) so that appropriate measures can be taken.

Moreover, a baseline blood sample need to be sent before the procedure (without waiting for its results) to enable better monitoring later on.

Table 1 – CSI Guidelines for Screening of risk for CI-AKI

Screening	Class	Level of evidence
Use e-GFR instead of S. creatinine alone	I	C
Use of risk score (e.g. Mehran et al)	I	B
Nephrology consult for eGFR ≤ 30 ml/min	I	C
Admit 12 hrs prior for eGFR ≤ 30 ml/min for hydration and continue it post procedure	I	C

Table 2 – Serum creatinine concentrations calculated by 2 different methods[a]

Serum Creatinine Concentration Calculation (mg/dL)[†]	Age (yr)					
	30	40	50	60	70	80
MDRD formula[‡]						
European Americans						
Men	1.47	1.39	1.34	1.30	1.26	1.23
Women	1.13	1.08	1.03	1.00	0.97	0.95
African Americans						
Men	1.73	1.65	1.58	1.53	1.49	1.46
Women	1.34	1.27	1.22	1.18	1.15	1.12
Cockcroft-Gault formula[$]						
Men	1.83	1.67	1.50	1.33	1.17	1.00
Women	1.56	1.42	1.28	1.13	0.99	0.85

MDRD = Modification of Diet in Renal Disease.
a Serum creatinine concentrations in various populations and ages corresponding to an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 calculated with the MDRD formula or a creatinine clearance of 60 mL/min calculated with the Cockcroft-Gault formula. Calculations assume a body weight of 72 kg and body surface area of 1.73 m^2. Reprinted from *Am J Kidney Dis*. Copyright 2002, with permission from the National Kidney Foundation.[39]

7. A (ii) Risks marker of CI-AKI (Table 6)

(i) **CKD**

CKD as a risk marker has been discussed previously.

Pre-existing renal insufficiency is the single greatest risk factor.[24,45] In one comprehensive review, an estimated 60% of patients with CI-AKI had pre-existing renal insufficiency.[45]

The more severe the baseline renal insufficiency, the greater the risk.[24,45] Although the risk of CI-AKI for a given serum creatinine value can vary widely, one can roughly estimate the percent risk by multiplying the serum creatinine concentration in mg/dL by 10.

(ii) **Diabetes mellitus** is often cited as a risk factor for CI-AKI,[45,46] but the risk ascribed to it is probably due to co-existing renal insufficiency, usually diabetic nephropathy, rather than to the diabetes per se.[45,46] In recent prospective studies, the incidence in patients with diabetes and normal renal function was similar to that in non-diabetic patients with normal renal function.[46,47]

On the other hand, patients with diabetes and preexisting renal insufficiency have a greater risk for contrast-induced nephropathy than non-diabetic patients with similar levels of preexisting renal insufficiency.[46,47] Moreover when patients in this high risk group develop nephropathy, they more often develop oliguria and need dialysis.[48] As with patients without diabetes, the risk of CI-AKI is directly proportional to the severity of preexisting renal insufficiency.

(iii) **Cardiovascular disease**

Extensive cardiovascular disease has been associated with increased risk for CI-AKI.

CHF is also associated with increased risk.[13,49,50]

Prior hypertension is independent predictor of CI-AKI in PCI Studies.[13,16,51,52] The risk for CI-AKI may be higher in patients with more extensive atherosclerotic disease, characterized by presence of peripheral vascular disease, [13,16,49] number of lesions,[53] or history of stroke or myocardial infarction.[51] Recently, there have been articles stating the role of statin therapy in significantly reducing the risk of CI-AKI.[54]

(iv) **Periprocedural hemodynamic instability**

Use of IABP, periprocedural hypotension,[13,50] LVF, primary PCI for AWMI[55] all increases risk of CI-AKI.

Use of IABP is a marker of hemodynamic instability, an indicator of procedural complications and a sign of severe

Table 3 – Risk factors predictive of abnormal serum creatinine

Which patients need creatinine screening?
Consider if patient has 1 of the following risk factor:
- Known renal insufficiency or renal disease
- Diabetes mellitus
- Advanced age
- Male sex
- Nephrotoxic drug use (furosemide)
- Chemotherapy of HIV infection
- Solitary kidney

HIV: human immunodeficiency virus.
Adapted from *Radiology*[42]

Table 4 – The Choyke questionnaire

Questions for patients:
1. Have you even been told you have renal problems?
2. Have you ever been told you have protein in your urine?
3. Do you have high blood pressure?
4. Do you have diabetes?
5. Do you have gout?
6. Have you ever had kidney surgery?

Adapted from *Tech Urol*.[43]

Table 5 – Emergency department risk factor screening

Patients with ≥ 1 risk factor should be considered at risk for CI-AKI:
- Age ≥ 60 yr.
- Diabetes mellitus
- Hypertension
- Coronary artery disease
- Congestive heart failure
- Severe liver disease

CI-AKI: contrast-induced nephropathy.
Adapted from *J Emerg Med*.[44]

atherosclerotic disease.[7,51,] Moreover, IABP also causes a risk of arthero-embolism to renal arteries.[7,51]

(v) **Nephrotoxic drugs**

NSAIDS, diuretics, amphotericin B, aminoglycosides, cisplatinum increase the risk for CI-AKI. So these drugs, to be avoided as far as possible.[56,57] Contradictory reports about ACEIs use and CI-AKI have come.[52,62] But one should continue their use, periprocedurally and should be discontinued on their standard contraindications only.

Moreover, when evaluating CI-AKI post procedurally in such patients, one should realize that ACEIs per se increase serum creatinine 10–25% from baseline if started recently.[58]

(vi) **Comorbidities**

a) **Anemia**

Low baseline hematocrit is a predictor of CI-AKI.[13] The threshold hematocrit at which the risk of CI-AKI increased was <41.2% in men and <34.4% in women. The mechanism explaining this is that the partial oxygen pressure of the outer medulla in kidneys is very low during normal function[23] and this is further lowered by contrast induced vasoconstriction and anemia causing hypoxia damage.

(vii) **Immonoglobinopathies**

Contrary to the previous reports of multiple myeloma being a risk factor for acute renal failure after contrast administration, McCarthy et al reviewed 7 series of 476 patients with multiple myeloma and found it not to be a major risk factor for ARF.[59]

Table 6 – Risk factors identified in multivariate analyses.

- Chronic kidney disease (stage III or greater; eGFR <60 mL/min/1.73 m^2)
- Diabetes mellitus (type 1 or type 2)
- Volume depletion
- Nephrotoxic drug use (NSAIDs, cyclosporine, aminoglycosides)
- Preprocedural hemodynamic instability
- Other comorbidities
  - Anemia
  - Congestive heart failure
  - Hypoalbuminemia

eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

(viii) **Volume of contrast media**

Some studies found a correlation between the volume of contrast given and the risk of nephropathy,[47,48,60] whereas other studies did not.[61]

Cigarroa et al[60] used a predetermined formula based on body weight and baseline renal function to limit the volume of contrast media in patients undergoing coronary angiography. The limit was 5 ml of contrast per kg of body weight up to maximum of 300 ml, divided by the serum creatinine in milligrams per deciliter. Nephropathy developed in 21% of the patients in whom the total volume of contrast exceeded the formula amount, compared with 2% ($P < 0.001$) of patients in whom the contrast volume fell within the prescribed limit.

(ix) **Additive Risks**

The effect of risk factors is additive. The identification of major risk markers for CI-AKI have allowed the development of risk models. The predictions used in published risk models are summarized in table 7–9.

As already discussed, the predicted incidence of both CI-AKI and Nephropathy requiring dialysis increases with the number of risk factors. One example of a risk scoring scheme is shown in the Figure 5.[50]

6 B. Use of contrast medium for RDA

Class I:

Use iso-osmolar contrast; or LOCM except Hexabrix/Omnipaque. (Level of Evidence A)
Prefer iso-osmolar for patients with diabetes and CKD. (Level of Evidence B)
Limit contrast volume < 100 ml for PCI or <30 ml for diagnostic (Level of Evidence B) (Level of Evidence C)
Staged procedure to be done 2 weeks apart (Level of Evidence C)

Class III:

Use of Gadolinium as an alternate to iodinated contrast (Level of Evidence B)

Types of contrast material. They are classified according to osmolality, which reflects the total particle concentration of the solution.

HOCM–2, 000mOsm/kg
LOCM–600–800mOsm/kg
IOCM–290mOsm/kg[64]

Though various properties of iodinated contrast agents such as osmolality, ionic nature, viscosity and iodine content have been incriminated for the potential renal toxicity, the osmolality in particular is considered to be the chief offender. So considerable efforts have gone through to decrease the

Table 7 – Comparison of published risk models

Population	McCullough et al[15,62]	Bartholomew et al[7]	Mehran et al[50]	Freeman et al[63]	Marenzi et al[55]
	PCI*/†	PCI	PCI	PCI†	Primary PCI for AMI
N	1,8261/1,869	20,479	8,357	16,592	208
Age (yr)	+	<60 ml/min	>75	>2 mg/dl	≥75
Proteinuria			>1.5 mg/dL or		
Abnormal S Cr			<60 ml/min/		
CrCl/EGFR			1.73 m^2		
IABP use	+	+	+	+	+
Emergency		+	+	+	
Diabetes		+	NYHA Class		
CHF		+	III–IV		
Hypertension'	+	+	+	Shock	≥300
Hypotension		+	+	+	+
PVD		>260	+	+	+
Contrast Volume (ml)					
Anemia					
Anterior AMI					
Time to reperfusion ≥6 hr					

AMI: acute myocardial infarction; CHF: congestive heart failure; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; NYHA: New York Heart Association, PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; S Cr: serum creatinine.
*Assumes contrast volume of 250 ml and mean age of 65 yr.
†Risk for nephropathy requiring dialysis.

osmolality of these agents and bring it as close to physiological as possible.

In the 1950s, only HOCM (e.g., diatrizoate) with osmolality 5–8 times that of plasma were used. In the1980s, LOCM agents such as iohexol, iopamidol, and ioxaglate, were introduced, having osmolality 2–3 times greater than that of plasma. In the 1990s, iso-osmolar non-ionic iodixanol with the same physiological osmolality as blood was developed. Red blood cell deformation, systemic vasodilation, intrarenal vasoconstriction, as well as direct renal tubular toxicity are all more common in contrast agents with osmolality greater than that of blood.

Earlier trials included comparisons between LOCM and HOCM, followed by comparisons between LOCMs and recently between IOCM and LOCM.

6(B)(I) LOCM vs HOCM

Theoretically sound, it was assumed that LOCM would reduce the incidence of CI-AKI over HOCM.

In the meta analysis by Barrett et al[28] of 31 randomized trials comparing LOCM and HOCM, LOCM were shown to significantly reduce the risk of a rise in serum creatinine of >0.5 mg/dl in patients with renal impairment (OR 0.5; CI, 0.36–0.68) but not in those with normal renal function (OR 0.75; CI, 0.52–1.1). In a prospective, randomized, double-blind multicenter trial by Rudnick et al[47] comparing LOCM, iohexol, and the HOCM, diatrizoate, in 1,196 patients undergoing cardiac angiography, renal function deterioration (increase in serum creatinine of >1 mg/dl, at 48–72 hr post-procedure) was observed in 7% of the patients receiving diatrizoate compared with 3% of the patients receiving iohexol ($p < 0.002$). Differences in nephrotoxicity between the two contrast groups were confined to patients with previous renal insufficiency or renal insufficiency with diabetes.

Thus in patients at increased risk of CI-AKI who are undergoing arterial administration of iodinated contrast medium, use of ionic high osmolality agents poses the greatest risk for development of CI-AKI.

(ii) LOCM vs LOCM

No significant differences among various LOCM's were observed in clinical trials.[65,66]

(iii) IOCM vs LOCM

A number of studies have evaluated whether an IOCM agent might provide a similar benefit over LOCM agents, but

Table 8 – CSI Guidelines for use of contrast medium in RDA

Use of contrast medium	Class	Level of evidence
Use iso-osmolar contrast; or LOCM except Hexabrix/Omnipaque	I	A
Prefer iso-osmolar for patients with diabetes and CKD	I	B
Limit contrast volume <100 ml for PCI or <30 ml for diagnostic	I	B & C
Staged procedure to be done 2 weeks apart	I	C
Use of Gadolinium as an alternate to iodinated contrast	III	B

Table 9 – Key Characteristics of Different Contrast Media

Generation Viscosity	Class	Type of Molecule	Examples	Lodinre (Mg1/ml)	Osmolarity (mOsm/kg-H_2O)	Viscosity At 37°C
First	High-osmolar	Ionic Monomer	Diatrizote (Hypaque)	370	2076	8.4
Second	Low-osmolar	Ionic Dimer	Ioxaglate (Hexabrix)	320	600	7.5
	Low-osmolar	Non-ionic Monomer	Iopamidol (Isovue)	370	796	9.4
			Iohexol (Omnipaque)	350	844	10.4
			Iopromide (Ultravist)	300	607	4.9
			Ioxilan (Oxilian)	350	695	8.1
			Ioversol (Optiray)	320	792	9.0
Third	Iso-osmolar	Non-ionic Dimer	Iodixanol (Visipaque)	320	290	11.8

no consensus has emerged at this point. In a pooled analysis of 16 double-blind, randomized, controlled trials (n = 2,727) comparing nephrotoxicity of IOCM iodixanol with LOCM,[67] CI-AKI occurred less frequently in the iodixanol than in the LOCM comparator group in all analyzed patients (1.4% vs 3.5%, P < 0.001). However, the majority of patients in this trial did not have CKD, and most subjects received one of the two LOCM; iohexol or ioxaglate.

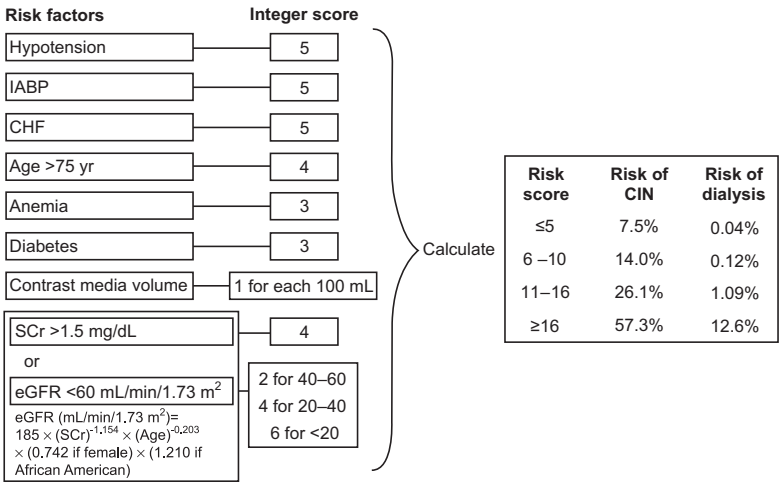
In both the Renal Toxicity Evaluation and Comparison Between Visipaque (iodixanol) and Hexabrix (ioxaglate) in Coronary Angiography in Renal Insufficiency (RECOVER) trial and A Prospective, Randomized, Placebo controlled trial of Ioxaglate versus Iodixanol in Patients at Increased Risk for Contrast Nephropathy (ICON) trial,[68] high risk patients with renal impairment were randomly assigned either to the IOCM agent iodixanol or the LOCM agent ioxaglate. In the RECOVER trial using a composite endpoint, the incidence of CI-AKI was significantly lower with iodixanol vs ioxaglate (7.9% vs 17.0%, p = 0.021),[69] while in the ICON trial, in-hospital acute renal failure occurred at similar rates in the iodixanol and ioxaglate groups (18.4% vs 22.2%, p = 0.80). In addition, there were no differences in mean increase in serum creatinine between the iodixanol and ioxaglate groups (0.20 mg/dl vs 0.35 mg/dl, p = 0.140) in the ICON trial.

This was the basis of the 2007 UA/NSTEMI guidelines which recommended that in patients with chronic kidney disease undergoing angiography, iso-osmolar contrast agents are indicated and are preferred. (Level of Evidence A)

However, in mid-2007, a major US randomized trial of contrast agents in patients with CAD and an estimated glomerular filtration rate of 20 to 59 ml/min who were undergoing angiography, the CARE study, was published.

In the randomized Cardiac Angiography in Renally Impaired Patients (CARE) study, rates of CI-AKI (defined by multiple endpoints) were similar in 414 angiography patients randomized to iodixanol or iopamidol, although mean changes in serum creatinine were higher in patients receiving the iso-osmolar agent (0.12 mg/dl vs 0.07 mg/dl, p = 0.03).[70] In the COntrast media and NephroToxicity following coronary Revascularization by AngioplaSTy (CONTRAST) study, CI-AKI was seen in 22.7% of the 162 patients randomized to iodixanol and in 27.7% of the 162 patients randomized to the low-osmolar agent iomeprol (p = 0.25).[71] Most recently, in the Visipaque Angiography/interventions with Laboratory Outcomes in Renal insufficiency (VALOR) study, the incidence of CI-AKI in 299 patients with CKD who underwent angiography was 21.8% in patients who were administered iodixanol and 23.8% in patients who were administrated the LOCM agent ioversol (p = 0.78)[72]

However, sub-analysis showed variations in relative renal safety by specific LOCM: A reduction in CI-AKI was observed when iodixanol was compared with ioxaglate, the only ionic

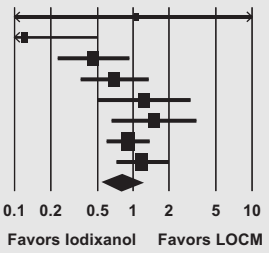


An example of a risk-scoring scheme and its application in predicting the risk for contrast-induced nephropathy (CIN) and CIN requiring dialysis.

Figure 5 – Mehran Risk Factor Scoring System

Table 10 – Forest plot of RR of CI-AKI of patients undergoing coronary angiography[73]

Study name	Procedure	LOCM	Year	Statistics for each study					CI-AKI/Total		Risk ratio and 95% CI
				Risk ratio	Lower limit	Upper limit	z-value	p-value	Group Iodixanol	Group Other	
Andersen	Coronary	ioxaglate	1993	1.056	0.069	16.251	0.039	0.969	1/36	1/38	
NEPHRIC	Coronary	iohexol	2003	0.119	0.029	0.496	-2.924	0.003	2/64	17/65	
RECOVER	Coronary	ioxaglate	2006	0.461	0.234	0.909	-2.236	0.025	11/140	23/135	
ICON	Coronary	Ioxaglate	2006	0.695	0.361	1.336	-1.091	0.275	12/71	18/74	
Feldkamp	Coronary	iopromide	2006	1.243	0.498	3.103	0.466	0.641	9/105	8/116	
CARE	Coronary	iopamidol	2007	1.511	0.669	3.414	0.993	0.321	14/210	9/204	
VALOR	Coronary	ioversol	2008	0.917	0.604	1.392	-0.408	0.683	34/156	34/143	
Juergens	Coronary	Iopromide	2008	1.194	0.732	1.950	0.711	0.477	25/91	23/100	
Overall				0.815	0.550	1.208	-1.017	0.309	I^2 = 21.34%		



LOCM (RR 0.58, CI 0.37–0.92. p = 0.02).[73] and with iohexol, a non-ionic

LOCM (RR 0.19–0.38, p < 0.01),[73,74] but no difference was noted in comparisons of iodixanol with iopamidol, iopromide, or ioversol,[73] and a single trial favored iomeprol.[75] A pooled comparison of iodixanol with all non-ionic LOCM other than iohexol indicated equivalent safety (RR 0.97; CI 0.72–1.32, p = 0.86).[74] Results were consistent regardless of ancillary preventive therapies (hydration, acetylcysteine), route of administration (intravenous or intra-arterial), age, sex, dose or preexisting CKD or diabetes. Of further interest, findings were similar in the 8 studies (n = 1793 patients) performed in the setting of coronary angiography, as shown in Table 10–15.[73]

These more recent observations indicate that the CI-AKI risk of contrast media cannot be attributed to osmolarity alone, but that ionicity and other and unknown characteristics of specific agents may play a role. Thus, the updated evidence base suggests that the recommended choices of contrast media during coronary angiography be expanded to either iso-osmolar media or LOCM other than ioxaglate or iohexol.

Table 11 – CSI Guidelines for Risk Reduction Strategies for CI-AKI

Risk reduction strategies for CI-AKI	Class	Level of Evidence
Withholding nephrotoxic drugs e.g., NSAID, loop diuretics 24–48 hrs prior to the procedure	I	B
Adequate intravenous volume expansion with isotonic crystalloids (1.0–1.5 ml/kg/hr) for 3–12 hrs before procedure and continued for 6–24 hours afterwards lessens the risk of CI-AKI	I	A
Admit 12 hrs prior for eGFR ≤ 59 ml/min for hydration	I	B
Use of half normal saline in hypertensive patients	II a	C
N-acetylcysteine	II b	B
Prophylactic hemofiltration	II b	B
Ascorbic acid	II b	B
Statins	II b	B
Theophylline/Aminophylline	II b	B
Coronary sinus withdrawal of blood	II b	C
Sodium bicarbonate	II b	
Prophylactic hemodialysis	III	B
Fenoldopam, dopamine, calcium channel blockers, l-arginine	III	
Furosemide, mannitol	III	

Table 12 – Overview of randomized trials on the use of prophylactic hydration

Study	Patient numbers	Renal function inclusion criteria Mean serum creatinine Mean contrast medium volume Diabetes mellitus	Fluid protocol	Outcome
1	2	3	4	5
Solomon et al 1994 [104]	78	Serum creatinine ≥1.6 mg/dl or CrCl ≤ 60 ml/min 2.1 mg/dl 129 ml 53%	Group 1: 0.45% NaCI 1 ml/kg body weight per h 12 h before to 12 h after procedure Group 2: idem + mannitol 25 g i.v, 1 h before angiography Group 3: idem + 80 mg furosemide i.v. 30 min before procedure	Increase serum creatinine ≥0.5 mg/dl within 48 h: Group 1:11%, Group 2: 28%, Group 3: 40%; P = 0.02
Taylor et al 1998 [109]	36	Serum creatinine 1.4–3 mg/dl or Cr CI 25–60 ml/min 1.75 mg/dl 175 ml 39%	Group 1 'in-patient'; 0.45% NaCI 75 ml/h 12 h before to 12 h after procedure Group 2 'outpatient': 1000 ml oral clear liquid over 10 h + 0.45% Nad 300 ml/h from 30 to 60 min before procedure during 6 h	Increase serum creatinine within 48 h: Group 1: 0.21 ± 0.38 mg/dl, Group 2: 0.12 ± 0.23 mg/dl; P = NS
Mueller et al 2002 [112]	1383	Not on dialysis 0.93 mg/dl 234 ml 16%	Group 1; 0.9% NaCI Group 2: 0.45% NaCI in 5% glucose Both at 1 ml/kg body weight per h from 8 a.m. before to 8 a.m. after procedure	Increase serum creatinine ≥ 0.5 mg/dl within 48 h: Group 1: 0.7%, Group 2: 2.0%; P = 0.04 Mortality at 30 days, cardiac and vascular complications; P = NS
Trivedi et al 2003 [108]	53	CrCI > 20 ml/min 1.21 mg/dl 194 ml 19%	Group 1: 0.9% NaCI 1 ml/kg body weight per h for 12h before and 12 h after procedure Group 2: unrestricted oral fluids	Increase serum creatinine ≥0.5 mg/dl within 48 h: Group 1: 3.7%, Group 2: 34.6%; P = 0.005
Krasuski et al 2003 [114]	63	Serum creatinine 1.6–3.0 mg/dl 1.8 mg/dl 134 ml 54%	Group 1: bolus of 250 ml 0.9% NaCI 20 min before procedure, 0.45% NaCI 1 ml/kg body weight per h for 12 h after procedure Group 2: 0.45% NaCI in 5% glucose 1 ml/kg body weight per h > 12 h before to 12 h after procedure	Increase serum creatinine ≥ 0.5 mg/dl within 48 h: Group 1; 10.8%, Group 2: 0%, P = 0.136
Bader et al 2004 [110]	39	Serum creatinine 0.6–1.2 mg/dl 0.9 mg/dl 211 ml 26%	Group 1: 300 ml 0.9% NaCI during procedure Group 2: >2000 ml 0.9% NaCI 12 h before to 12 h after procedure	Mean decrease in glomerular filtration rate after 48 h: Group 1 : 34.6 ± 25.7 ml/min per 1.73 m^2 Group 2: 18.3 ± 25.0 ml/min/ 1.73 m^2, p < 0.05 Decrease in glomerular filtration rate >50% within 48 h Group 1: 15%, Group 2: 5.3%; P= 0.605
Merten et al 2004 [116]	119	Serum creatinine 1.1–8 mg/dl 1.8 mg/d) 132 ml 48%	Group 1: 157 mEq/L NaHCOs in 5% glucose 3 ml/kg body weight per h - maximum 330 ml - 1 h before and 1 ml/kg body weight per h - maximum 110 ml - 6 h after procedure Group 2: idem with 0.9% NaCI	Increase serum creatinine >25% within 48 h: Group 1: 1.7%, Group 2: 13.6%; P = 0.02
Dussol et al 2006 [115]	153	CrCI 15–60 ml/min 2.25 mg/dl 118 ml 32%	Group 1: 1 g/10 kg body weight per day NaCI *per os for* 2 days before procedure Group 2: 0.9% NaCI i.v. at 15 ml/kg body weight for 6 h before procedure	Increase serum creatinine ≥ 0.5 mg/dl Group 1: 6.6% Group 2: 5.2%; P = NS

CrCl: creatinine clearance; iv: Intravenously; NS: not significant.
To convert serum creatinine in mg/dl to μmol/l multiply by 88.4.

Table 13 – Overview of meta-analyses on the prophylactic effect of acetylcysteine

Study	Number of trials/ number of patients	Relative risk (95% confidence interval), P value	Author conclusions
Isenbarger et al (2003) [128]	7/805	0.37 (0.16-0.84), P = NA	Treatment beneficial. The effect sizes of the trials were heterogeneous, but there was no evidence of publication bias
Birck et al 2003 [127]	7/805	0.435 (0.215 – 0.879), P = 0.02	Treatment beneficial. Evidence of publication bias (absence of small trials with negative results). Heterogeneity across the trials
Guru and Fremes 2004 [136]	11/1213	0.46 (0.32 – 0.66), P = NA	Treatment beneficial. Heterogeneity across the trials
Misra et al 2004 [137]	5/643	0.30 (0.11–0.82), P = NA	Treatment beneficial. Heterogeneity across the trials
Alonso et al 2004 [129]	8/885	0.41 (0.22–0.79), =0.007	Treatment beneficial. Heterogeneity across the trials with respect to patient population, procedure and definition of CI-AKI. Limited to summary measures of unadjusted CI-AKI rates
Bagshaw and Ghali 2004 [130]	14/1261	0.54 (0.32–0.91), P = 0.02	Inconclusive. Heterogeneity across the trials. Evidence of publication bias
Pannu et al 2004 [131]	15/1776	0.65 (0.43–1.00), P = 0.049	Inconclusive. Heterogeneity across the trials. Evidence of publication bias. No statistically significant effects in several prespecified subgroup analyses. The results were not robust to the addition of hypothetical new or unidentified randomized trials
Kshirsagar et al 2004 [132]	16/1538	NA, P=NA	Inconclusive. Heterogeneity across the trials. No evidence of publication bias. Research on acetylcysteine and the incidence of CI-AKI is too inconsistent at present to warrant a conclusion on efficacy or a recommendation for its routine use
Nallamothu et al 2004 [133]	20/2195	0.73 (0.52–1.0), P = 0.08	Inconclusive, Heterogeneity across the trials. Borderline evidence of publication bias. Higher-quality trials demonstrated a stronger benefit for acetylcysteine in general
Liu et al 2005 [134]	9/1028	0.43 (0.24–0.75), P = NA	Treatment beneficial. Significant heterogeneity existed among studies, suggesting differences in patient populations or study methodology not identified by sensitivity analyses
Duong et al 2005 [135]	14/1584	0.57 (0.37–0.84), P = 0.01	Treatment beneficial. Heterogeneity across the trials. We identified only one important difference between the positive and the negative studies: the cumulative exposure to contrast media (174 vs 152 ml). In the trials showing benefit for acetylcysteine, the treated patients' postprocedure serum creatinine unexpectedly decreased by 0.21 mg/dl
Zagler et al [138]	13/1892	0.68 (0.46–1.01), P = NA	Inconclusive. Heterogeneity across the trials. The meta-analysis is neither conclusive nor provides proof beyond a reasonable doubt to influence clinical practice and public policy

(iv) **Volume of Contrast medium**

The evidence suggests that the risk of CI-AKI increases with the volume of contrast within a particular class (even the isomolar is not exempted).[7,13,16,48,49,52,55,63,76,77]

However the data are not completely consistent.[76–84] In patients with normal renal functions, higher volumes of contrast agent cause no significant changes in renal functions, particularly with intravenous administration.[78]

However, in patients with advanced renal disease, even volumes (<30 ml) can cause CI-AKI. [48]

Generally, a volume of contrast medium of no more than 100 ml is preferable for patients, with an eGFR lower than 60 ml/min/1.73 m^2.[41]

As a general rule, the volume of contrast received should not exceed twice the baseline level of eGFR in ml. [87]

CI-AKI is infrequent if contrast volume administrated is less than the adjusted contrast volume.[60,88]

Adjusted contrast volume = (5 ml × body weight (kg))/ baseline serum creatinine.

Similarly, the ratio of contrast medium volume to creatinine clearance has recently been suggested to be a more

Table 14 – Outlines the recommendation of interventions commonly used to reduce the risk of CI-AKI

Intervention	Details	Evidence	Comments	Recommendation
Intravenous saline therapy	Intravenous 0.9% saline at 1 ml/kg/hr for 24 hr, beginning 2–12 hr before administration of contrast medium	Several small randomized trials that compared intravenous saline with oral fluids alone, shorter regimens of intravenous fluid, or 0.45% saline	Optimal duration of intravenous therapy not fully established by existing trials	Generally recommended
Contrast medium Type	Low osmolality	Meta-analysis of several randomized controlled trials comparing low-osmolar with high-osmolar contrast mediums	Further data on the relative nephrotoxicity of iso-osmolar contrast mediums are required	Low-osmolality mediums recommended
Dose	Lowest required to complete the procedure	Cohort studies that associate higher doses with greater risk	A dose >5 ml × kg of body weight ÷ serum creati-nine level in mg/dl associated with higher risk	Lowest dose possible recommended
Intravenous sodium bicarbonate	Intravenous sodium bicarbonate 154 mmol/liter at 3 ml/kg/hr before administration of contrast medium, then 1 ml/kg/hr for 6 hr after administration	A single randomized controlled trial that suggested a lower risk of an increase of >25% in creatinine levels with bicarbonate as compared with 0.9% saline given at the same rate of infusion and duration	Methodologic flaws in the trial	Not generally recommended unless efficacy confirmed by further trials
N-acetylcysteine	Most commonly, 600 mg by mouth every 12 hr for four doses, beginning before administration of contrast medium	Multiple randomized trials and meta-analyses	Inconsistent trial results for unknown reasons: optimal dose not clear	Not generally recommended pending further data to confirm efficacy

*Several other agents, such as captopril, have been studied in small trials, but data are insufficient to support their use at present.

accurate predictor of Acute Kidney Injury (AKI) than other factors, a ratio higher than 3.7 is associated with increased risk.[87] So in patients at risk (eGFR < 60 ml/min/1.73 m^2) reduce volume of contrast agent to <30 ml for diagnostic catheterization and <100 ml for PCI to reduce CI-AKI.

(vi) **Route of Administrations**

A number of studies have provided circumstantial evidence that the risk of CI-AKI is higher after intra-arterial compared with intravenous administration.[89]

The meta-analysis comparing HOCM and LOCM suggested that the reduction in risk for CI-AKI with LOCM vs. HOCM was significant for intra-arterial administration but not for intravenous administration.[28]

Risk for CI-AKI is maximum for injections into abdominal aorta and renal arteries. This risk decreases as one moves into aortic arch or more proximally.

Risk is lowest for intravenous injections below renal arteries as they are diluted the most (after mixing well with blood).

Athero-embolism may also be the reason for higher incidence of CI-AKI after arterial administration.

Table 15

Follow-up procedure following angiography	Class	Level of evidence
Rpt S. creatinine 72 hrs later for eGFR < 59 ml/hr	I	B

(vii) **Staged Procedures**

Repeat contrast administration is risk factor for CI-AKI.[90,91] A study of serial serum creatinine levels over time showed that renal impairment may persist for ≥10 days after contrast injection.[92] This fits with observations that the recovery phase after ischemic acute renal failure—characterized by redifferentiation and repolarization of tubular cells and recovery of GFR—typically begins about 8 days after the ischemic insult.[93] These findings suggest that it is desirable to allow sufficient time for renal function to return to normal before subjecting the kidneys to further insult.

It is therefore recommended that, when possible, 2 weeks should be allowed between procedures, because this corresponds to the expected recovery time for the kidney after an acute insult.

(viii) **Gadolinium as an alternative**

Multiple reports and case series have been inconclusive with gadolinium used as an alternative to iodinated contrast media in patients with impaired renal function.[94–98]

A recently published clinical study supports this conclusion. In patients with renal impairment undergoing percutaneous coronary intervention (PCI), the use of gadolinium based contrast agent did not protect against CI-AKI; the incidence of CI-AKI was higher in those receiving gadolinium that in a group of matched controls receiving iso-osmolar contrast.[99]

(viii) **CO_2 as an alternative**

CO_2-based angiography is not approved as it suffers from drawbacks of poor quality images, delivery system, patient positioning and safety issues.[100,101]

6(C) Risk reduction strategies for CI-AKI

Class I
- Withholding nephrotoxic drugs e.g., NSAID, loop diuretics 24–48 hrs prior to the procedure. (Level of Evidence B)
- Adequate intravenous volume expansion with isotonic crystalloids (1.0 to 1.5 ml/kg/hr) for 3–12 hrs before procedure and continued for 6–24 hours afterwards lessens the risk of CI-AKI. (Level of Evidence A)
- Admit 12 hrs prior for eGFR $\leq$59 ml/min for hydration (Level of Evidence B)

Class IIa
- Use of half normal saline in hypertensive patients (Level of Evidence C)

Class IIb
- N-acetylcystiene (Level of Evidence B)
- Prophylactic hemofiltration (Level of Evidence B)
- Ascorbic acid (Level of Evidence B)
- Statins (Level of Evidence B)
- Theophylline/aminophylline (Level of Evidence B)
- Coronary sinus withdrawal of blood (Level of Evidence C)
- Sodium bicarbonate

Class III
- Prophylactic hemodialysis (Level of Evidence B)
- Fenoldopam, dopamine, calcium channel blockers, l-arginine
- Furosemide, mannitol

(i) **Withholding nephrotoxic drugs.** Hold NSAIDs, high dose loop diuretics, aminoglycosides, etc. 24–48 hrs prior to the procedure and can be re-introduced 24 hrs thereafter.[56]

Metformin needs to be withheld to avoid lactic acidosis, should AKI develop. ACEI/ARBs can be however continued.[57]

(ii) **Intravenous volume expansion**

It has a definite role in reducing risk of CI-AKI.

The theoretical rationale for hydration is that it should decrease the activity of the renin-angiotensin system, reduce the levels of other vasoconstrictive hormones such as endothelin, increase sodium diuresis, decrease tubuloglomerular feedback, prevent tubular obstruction, protect against reactive oxygen species, and dilute the contrast media in the tubule, thus decreasing any direct nephrotoxic effect of the contrast agent on the tubular epithelium.[102]

Several studies in animals demonstrated hydration with saline infusions to be beneficial in preventing CI-AKI.[103]

Early clinical studies used historical controls for comparison and also suggested that hydration is beneficial. Subsequently, intravenous hydration became the standard method to prevent CI-AKI.[45,46]

There have been a few prospective randomized studies comparing saline alone vs other therapies as prophylactic strategies.[25,104–107]

Solomon et al[104] randomized patients with chronic kidney disease undergoing cardiac angiography to receive either saline alone, saline and mannitol, or saline and furosemide. All three groups received 0.45% saline intravenously at 1 ml/kg/hr for 12 hrs before and 12 hrs after receiving contrast. Nephropathy occurred in 11% of patients receiving saline alone vs 28% who received saline and mannitol and 40% who received saline and furosemide.

Different regimens of saline hydration have been used, but no one regimen has demonstrated clear superiority.

Trivedi et al[108] prospectively randomized patients undergoing cardiac angiography to receive either intravenous saline for 12 hrs both before and after catheterization or oral fluids only, taken as desired. CI-AKI occurred in 3.7% of those who received intravenous saline vs 34.6% of those who received only oral fluids.

In contrast, the Preparation for Angiography in Renal Dysfunction (PREPARED) trial[109] showed that in patients with chronic kidney disease undergoing coronary angiography, hydration on an outpatient basis before catheterization, coupled with a brief period of intravenous hydration, was equivalent to overnight intravenous hydration.

Bader et al [110] randomized patients undergoing computed tomography or digital angiography to receive either 2,000 ml of intravenous fluid over 24 hrs (12 hrs before and 12 hrs after contrast) or 300 ml of intravenous fluid during the radiologic procedure. The glomerular filtration rate fell by 18.3 ml/min in the continuous infusion group compared with a 34.6 ml/min fall in the bolus infusion group ($p < 0.05$), suggesting that slow hydration is superior to bolus expansion during the procedure.

The prevention of Radio Contrast Induced Nephropathy Clinical Evaluation (PRINCE) study[111] tested the hypothesis that forced diuresis with maintenance of intravascular volume would result in less contrast induced renal injury. Although no difference in the incidence of CI-AKI was observed between patients who underwent forced diuresis and those who did not, the incidence in participants with urine flow rates greater than 150 ml/hr was 21.6% vs 45.9% in those with lower urine flow rates ($P = 0.03$).

Mueller et al [112] compared the use of isotonic (0.9%) saline ($n = 685$) vs half-isotonic (0.45%) saline ($n = 698$) in patients undergoing coronary angioplasty. Both groups received about 2,000 ml of intravenous fluid. The incidence of CI-AKI was significantly lower with isotonic saline (0.7%) than with half-isotonic saline (2%, $P = 0.04$).

Generally a regimen of intravenous .9% saline at 1 ml/kg/hr for 24 hrs, beginning 2–12 hrs before administration of contrast medium is recommended to achieve a urine flow rate of at least 150 ml/hr.

Although volume supplementation with saline should be considered in all patients undergoing contrast medium exposure during diagnostic or therapeutic coronary procedures, patients with chronic kidney disease and impaired left ventricular systolic function should receive cautious hydration. For patients with moderate/severe reductions in left ventricle ejection fraction, we recommend hydration with 0.45% saline matching the urine output to maintain a euvolemic state.[113]

45% saline may also be recommended in severely hypertensive patients for the fear of precipitating hypertensive crises with 0.9% saline.

(iv) **Sodium bicarbonate: Data are preliminary**

Merten et al,[116] in a randomized controlled trial at a single center, compared hydration with sodium bicarbonate vs sodium chloride to prevent CI-AKI in azotemic patients receiving low osmolar contrast agents. Both infusions contained 154 mEq of either sodium chloride or sodium bicarbonate in 1 L of 5% dextrose and water. A close approximation of the sodium bicarbonate solution can be achieved by adding 3 ampules (150 mEq) of sodium bicarbonate to 1 L of 5% dextrose in water: the final sodium bicarbonate concentration is 130 mEq/L. The infusion rate for either fluid was 3 mL/kg/hour for 1 hour before contrast administration, followed by 1 ml/kg/hr during contrast administration and then for 6 hours afterward.

CI-AKI occurred in 1.7% of patients who received sodium bicarbonate compared with 13.6% of patients who received sodium chloride ($P = 0.02$).

The benefit of sodium bicarbonate in preventing CI-AKI is probably not simply due to volume expansion, which was similar between treatment groups. The authors postulated instead that sodium bicarbonate may reduce the formation of oxygen free radicals (a pH-dependent reaction), previously reported to play a pathogenetic role in CI-AKI.[116]

Four recent meta-analyses[117–120] evaluating the protective effects of hydration with $NaHCO_3$ compared with hydration with normal saline have shown $NaHCO_3$ to be more effective in preventing CI-AKI by 54–63%: (RR: 0.37, 95% CI: 0.18–0.74); (RR: 0.45; 95% CI; 0.26–0.79); (RR: 0.46; 95% CI: 0.26–0.82); and (RR: 0.52; 95% CI: 0.34–0.80).

(v) **Hemodialysis and Hemofiltration**

Numerous studies have demonstrated that 2–3 hours of hemodialysis effectively removes 60–90% of contrast medium.[121] Several studies explored the prophylactic value of hemodialysis in high risk patients, but most failed to demonstrate a reduced incidence of CI-AKI.[121]

On the other hand, Marenzi et al[122] recently found that hemofiltration significantly reduced CI-AKI in patients at high risk. In this study, patients with chronic kidney disease undergoing coronary angiography were randomized to undergo either hemofiltration in an intensive care unit or parenteral saline hydration. Hemofiltration was started 4–6 hours before contrast administration, stopped for coronary angiography, then resumed for an additional 18–24 hours. Isotonic saline was used as replacement fluid and was given at a rate of 1 L/hour, which matched the ultrafiltration rate so that no net fluid loss resulted. In the control group, isotonic saline was given at 1 ml/kg/hr for 6–8 hours before and 24 hours after angiography.

The incidence of CI-AKI was 5% in the hemofiltration group compared with 50% in the control group ($p < 0.001$). The in-hospital mortality rate was 2% in the hemofiltration group compared with 14% in the control group ($p = 0.02$).

Despite these impressive results, the conclusions of this study should be viewed with some caution. Removal of creatinine by hemofiltration per se could result in a lower incidence of CI-AKI, although this alone would not account for differences in mortality. Moreover, the mortality rate in the control group was inordinately high, suggesting that it was not a good representative cohort. Both groups received an extraordinary volume of contrast (approximately 250 ml) for patients with moderately sever chronic kidney disease (their baseline mean creatinine concentration was 3.0 mg/dl).

Conclusions

Given these reservations, due to the logistical effort and high cost associated with hemofiltration, larger randomized trials should be performed before this technique can be recommended as standard prophylaxis against CI-AKI in high-risk patients.

Somewhat related is the not infrequent clinical question of when to perform the next hemodialysis treatment in a patient undergoing chronic hemodialysis who receives intravascular contrast media. Although the question has not been extensively investigated in clinical trials, there is evidence that most patients can safely wait 24–36 hours after contrast exposure until their next hemodialysis treatment.

(vi) **PHARMACOLOGIC AGENTS**

With the exception of N-acetylcysteine, there are currently no approved pharmacological agents for prevention of CI-AKI.

(a) **ACETYLCYSTEINE**

There has been ongoing debate whether NAC is effective in the prevention of CI-AKI. N-acetylcysteine, a potent antioxidant that scavenges a wide variety of oxygen derived free radicals, may be capable of preventing CI-AKI, both by improving renal hemodynamics and by diminishing direct oxidative tissue damage.[123]

Several prospective, randomized trials showed that the administration of acetylcysteine along with hydration significantly reduced CI-AKI in high-risk patients, whereas other trials could not show a beneficial additional effect. What are the reasons for these contradictory results? Many prospective randomized trials used several different procedures, different types and volumes of contrast media, different timing and dosage of acetylcysteine administration, and different routes (intravenous or oral) of administration. The study by Briguori et al[124] emphasized the importance of acetylcysteine dosage. Their study indicated that the administration of a double dose of acetylcysteine (1200 mg twice daily) was superior compared with a standard dose of 600 mg twice daily. Baker et al[125] showed that the intravenous administration of high-dose acetylcysteine was also effective. However, some questions on the use of acetylcysteine arose from a nonrandomized study that investigated different markers of renal function after administration of acetylcysteine to healthy subjects without exposure to contrast agents. That study showed that in healthy subjects, acetylcysteine reduced serum creatinine by 3.5%, serum urea by 7.7%, and cystatin C concentrations by 1.3%. These

findings may indicate that acetylcysteine may also affect creatinine or urea metabolism.[126]

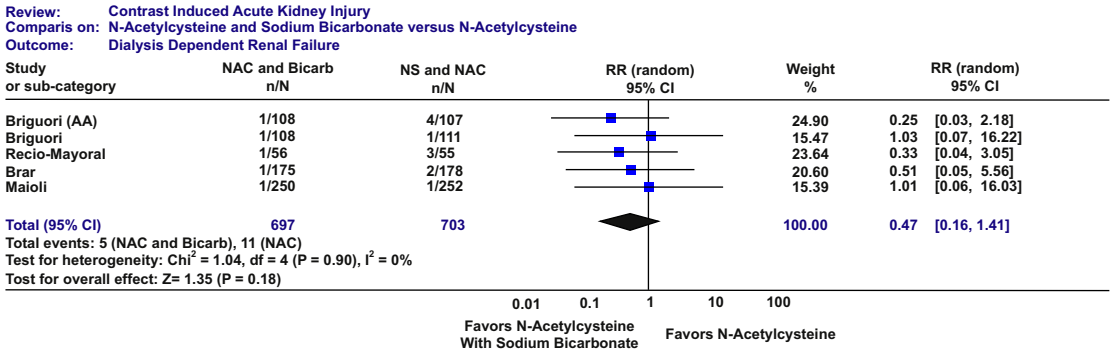
Acetylcysteine: Meta-analyses. Data from several meta-analyses[127–135] on the effect of acetylcysteine are summarized in Table 9.

The first meta-analysis by Birck et al[127] showed that compared with periprocedural hydration alone, the administration of acetylcysteine significantly reduced the risk of CI-AKI in patients with preexisting renal insufficiency. Isenbarger et al[128] reported a similar result. The meta-analysis by Alonso et al[129] including 8 prospective, randomized trials published in full-text articles and 4 additional studies published in abstract form, showed that acetylcysteine significantly reduces the risk for CI-AKI. Bagshaw and Ghali[130] analyzed 14 angiography trials including 1261 patients and reported a relative risk of 0.54 (95% CI, 0.32–0.91; P = 0.02). The meta-analysis by Pannu et al,[131] including 15 prospective, randomized trials, showed that acetylcysteine significantly reduced CI-AKI. However, these authors further noted a significant heterogeneity in the acetylcysteine effect across trials.[130,50] The meta-analysis of Kshirsagar et al,[132] including data from 15 published and 1 unpublished trial, described evidence of heterogeneity, thus precluding reliance on a meaningful summary effect estimate. Nallamothou et al[133] showed a non-significant trend toward benefit in patients treated with acetylcysteine. The meta-analysis by Liu et al,[134] analyzing 9 prospective, randomized trials, showed that acetylcysteine significantly reduced the risk of CI-AKI (relative risk, 0.43; 95% CI, 0.24–0.75). The recent meta-analysis of Duong et al[135] included 14 trials with 1584 patients and also showed that acetylcysteine significantly reduced the risk for developing CI-AKI (relative risk, 0.57; 95% CI, 0.37–0.84; P < 0.01).

Recently, Kelly et al[139] performed a meta-analysis of NAC compared with hydration alone. They found that oral or intravenous NAC significantly reduced CI- AKI by 38% when compared with hydration controls (RR: 0.62; 95% CI: 0.44–0.88). Another recently published meta-analysis[140] focused on the question of combined hydration and prophylaxis with both $NaHCO_3$ and NAC, demonstrating a significant benefit for combination prophylaxis over NAC with or without hydration alone in reducing the occurrence of CI-AKI but not dialysis dependent renal failure.

However, a recent large randomized trial (N = 2308)[141] found that acetylcysteine does not reduce the risk of CI-AKI or other clinically relevant outcomes in at-risk patients undergoing coronary and peripheral vascular angiography. Consistent effects were observed in all subgroups analyzed, including those with renal impairment.

Though the ESC guidelines recommends NAC as a Class III indication, on the basis of evidence cited above we will like to classify it under Class IIb.



University of Vermont has proposed an algorithm for acute kidney injury prophylaxis as outlined below

University of Vermont:
Acute Kidney Injury Prophylaxis Protocol

- Eligibility determined by Creatinine > 1.5 or estimated GFR Less than 60
- N-acetylcysteine 1200 mg po bid- 2 doses prior to cath and 2 doses post for inpatients. For outpatients, this is optional.
- Stop Metformin
- Diuretics and NSAIDs stopped 24 hour before to 24 hour after contrast administration (may resume diuretics if concern regarding CHF)
- IV Isotonic Bicarbonate at 3 ml/kg/h x approximately 1 hour before and 1 ml/kg/h x 6 hour after contrast exposure
- NPO for approx. 3 hours prior to procedure; do not use "NPO after Midnight"—can make NPO after 5:00 AM as a routine.

Figure 6 – Individual randomized controlled trials are listed in order by year of publication. Outcome is dialysis. The size of each square denotes the weight of each trial's RR in calculating the combined RR. The diamond represents the combined RR at the center; opposing points of the diamond represent the 95% CIs. Treatment: NAC plus Bicarb.

(b) **Other prophylactic regimens**

Theophylline/aminophylline—Not recommended at this time. Several reports suggest that theophylline, an adenosine antagonist, prevents CI-AKI.[142,143]

Erley et al[143] randomized 39 patients who received contrast media to receive either intravenous theophylline or placebo. Although no patient in either group developed CI-AKI, the glomerular filtration rate decreased in the placebo group from 88 ml/min at baseline to 75 ml/minute 4 hours after contrast administration; it remained unchanged in the theophylline group.

In several other placebo-controlled studies, theophylline (given orally or intravenously) prevented contrast induced falls in creatinine clearance, but all the studies were in low risk patients, and CI-AKI was not seen in any groups.

Theophylline has potential risks, including ventricular arrhythmias, seizures, and shock-all of which may be potentiated by a variety of other drugs.[142]

Conclusions

The data regarding theophylline are mixed. Favorable studies were limited by small numbers, absence of high-risk patients, and a failure to demonstrate differences in the incidence of CI-AKI. Therefore, theophylline cannot be recommended as standard prophylaxis against CI-AKI at this time.

(c) **Statins**

Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses and stabilization of atherosclerotic plaques. These and several other emergent properties could act in concert with the potent low-density lipoprotein cholesterol lowering effects of statins to exert early as well as lasting cardiovascular protective and potentially reno-protective effects.[144]

Some retrospective series analyzed the efficacy of pretreatment with statins on the development of CI-AKI in patients undergoing cardiac catheterization.[145,146]

In the large series by Khanal et al with 29,409 patients exposed to contrast media during diagnostic and therapeutic procedures, pretreatment with statins was associated with a lower incidence of CI-AKI (4.4% vs 5.9%, $p < 0.0001$) and requirement of dialysis (0.32% vs 0.49%, $p = 0.03$).[145] However in the Prevention of RadiOcontrast Medium-Induced nephropathy using Short-term high-dose Simvastatin (PROMISS) trial.[147] Of 247 patients with chronic renal insufficiency undergoing coronary angiography pre-treatment with simvastatin (40 mg orally every 12 hours starting the evening before and ending the morning after the procedure), the incidence of CI-AKI was quite similar in the treatment arm and the placebo arm (2.5% vs 3.4%, $p = 1.00$).

However recently a subgroup analysis[52] of the ARMYDA-CI-AKI trial lend further support to early use of high-dose statins as adjuvant pharmacologic therapy before percutaneous coronary revascularization to reduce the incidence of CI-AKI.

(d) **Ascorbic acid**

Ascorbic acid has been tested in a multicenter, blinded, placebo-controlled trial and been shown to reduce rates of CI-AKI. The dose of ascorbic acid (vitamin C over the counter) used in this trial was 3 g orally the night before and 2 g orally twice a day after the procedure.[148] However, a second large well-designed trial (the REMEDIAL trial)[149] found that ascorbic acid did not provide added benefit to a prophylactic regimen of isotonic saline plus NAC among patients at high risk for CI-AKI. In summary, data are insufficient to support the use of ascorbic acid for the prevention of CI-AKI.

(e) **Dopamine**

Due to its dilatory effect on the renal vasculature and the ability to increase the renal blood flow and glomerular filtration rate, dopamine was thought to be useful in the prevention of CI-AKI. However, results of clinical studies are conflicting.[150,151] Moreover, in patients with peripheral vascular disease and CI-AKI, the effect of dopamine on renal function was found to be deleterious.[152]

(f) **Fenoldopam**

Fenoldopam, a selective dopamine-1 receptor agonist known to produce both systemic and renal arteriolar vasodilatation, was shown to blunt the decline in renal blood flow and GFR in animals exposed to contrast media.[153] In the largest randomized radiocontrast study to date, the Fenoldopam Mesylate for the Prevention of Contrast Induced Nephropathy (CONTRAST),[107] 315 patients undergoing invasive cardiac procedures with a calculated CrCl < 60 ml/min were hydrated and then randomized to either placebo or fenoldopam starting 1 hour before catheterization and continuing until 12 hours after. The incidence of CI-AKI, occurred in 33.6% of the fenoldopam group vs 30.1% of the control patients ($p = 0.54$). Thus, fenoldopam cannot be recommended for prophylactic use in patients at high-risk for CI-AKI.

(g) **Loop diuretics**

Oliguria is generally recognized as a bad prognostic sign in patients with incipient or established AKI. The temptation to increase urine output in patients with or at risk for AKI is therefore great.

Two recent meta-analyses[154,155] and one recent review[156] concluded that loop diuretics were neither associated with improved survival benefit in AKI nor with better recovery of renal function despite reduction in the oliguric period.

Furthermore, Mehta et al. [157] found that diuretic use was associated with significantly increased risk of death or non-recovery of renal function. Loop diuretics may, however, convert an oliguric into a non-oliguric form of AKI that may allow easier fluid and/or nutritional support of the patient.

Loop diuretics in the setting of impaired renal function are not without hazards. Transient episodes of tinnitus and/or vertigo and very rarely deafness may be present if high doses are administered intravenously in <6 h.

Based on these data, it can be concluded that there is no evidence to support the use of loop diuretics in the prevention of ARF.

However a new system-Renal Guard System aims to match fluid input to output and promote urination with only limited use of loop diuretics. The device is "an automated hydration-matching system" that maintains high urine output (the target >300 mL/h) during use of contrast agents but avoids the negative fluid balance that can result from the high-dose furosemide diuresis used to facilitate urinary contrast elimination (which is thought to attenuate the risk of CI-AKI).

The second Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL 2)[158] randomized patients considered high risk for CI-AKI to have their coronary- or peripheral-artery catheterizations—diagnostic, therapeutic, or a combination of the two—accompanied by sodium-bicarbonate-based hydration or hydration with the Renal-Guard system (PLC Medical Systems). All procedures used the iso-osmolar contrast agent iodixanol (Visipaque, GE Healthcare).

Laboratory markers of renal injury were significantly less likely to be increased over 48 hours among RenalGuard-managed patients, who were also significantly less likely to go on dialysis within one month.

(h) Mannitol

Several small trials have investigated the effect of mannitol added to fluids in the prevention of CI-AKI. In one trial, 78 patients with stable chronic renal failure about to undergo coronary angiography were randomly assigned to one of three regimens .102One of the regimens added mannitol to half-isotonic saline. The incidence of AKI (defined as a rise in the S. creatinine of at least 0.5 mg/dL) was lowest in the group treated with saline alone, and mannitol was of no added benefit.

In another study,[105] patients were randomly assigned to receive saline or one of three renal vasodilator/diuretic drugs [dopamine (2 μg/kg/min), mannitol (15 g/dL in a one-half isotonic saline solution given at 100 mL/h) or atrial natriuretic peptide (ANP)]. Dopamine, mannitol and atrial natriuretic peptide were associated with a much higher incidence of renal dysfunction in diabetic subjects.

(i) Natriuretic peptides

Synthetic analogues of ANP have shown promise in the management of AKI in the laboratory setting. To date, this promise has failed to translate into clinically apparent benefit, and a large multicenter, prospective RCT of anaritide, a synthetic analog of ANP, could not show clinically significant improvement in dialysis-free survival or overall mortality in patients with AKI.[159] Ularitide (urodilantin) is a natriuretic pro-ANP fragment produced within the kidney. In a small randomized trial, ularitide did not reduce the need for dialysis in patients with AKI.[160]

(j) Calcium channel blockers

Calcium channel blockers have been evaluated for reduction in the risk for CI-AKI because of their vasodilatory properties. Nifedipine,[161–163] nitrendipine,[164–166] felodipine,[167] and amlodipine[168] have all been tested in small studies in patients at risk for CI-AKI with no consistent evidence of benefit.

(k) Targeted renal therapy

Targeted renal therapy (TRT) is a novel catheter-based approach aimed at delivering renal vasodilating agents such as fenoldopam and nesiritide (a B-type natriuretic pepetide) directly to kidney via the renal arteries using the Benephit ™ infusion system (Flow Medica, Inc., Fremont, CA) to maximize the beneficial renal effects of the drugs while minimizing the systemic side effects.[169]

Teirstein et al[170] conduced a pivotal study that proved the concept of intra-renal(IR) fenoldopam in patients undergoing coronary angiography and angioplasty. Compared with intravenous fenoldopam, IR administration was associated with a significant increase in GFR (73.7 ml/min vs 62. 6 ml/min, $p = 0.0007$; measured by inulin clearance) and renal plasma flow (537.2 ml/min vs 494.0 ml/min, $p < 0.01$; measured by PAH clearance) and a decrease in the fenoldopam plasma levels (3.3 ng/ml vs 4.8 ng/ml, $p < 0.0001$). Even though this was a mechanistic study, the results suggest that the initial vaso-constrictive insult from contrast media may be averted by infusion of the powerful vasodilating agent fenoldopam during contrast media-associated procedures.

Two recent studies by Allie et al[171,172] have shown that percutaneous delivery of fenoldopam directly into renal arteries appears to prevent CI-AKI in patients undergoing peripheral vascular intervention or endovascular aortic aneurysm repair[171] (EVAR),and also seems to have protective effect in patients undergoing coronary artery bypass graft surgery.[172] The largest experience so far with the TRT concept and IR administration of fenoldopam was described in the Be-RITE! registry.[173] In a focused group of 285 high-risk patients who were followed for at least 48 hours after a coronary or peripheral contrast-associated procedure, the results were encouraging .The author compared the actual observed rate of CI-AKI to the rates that can be predicted by Mehran score. The incidence of CI-AKI was 71% lower than the predicted by the Mehran score (8.1% actual CI-AKI vs 28.0% predicted, $p < 0.0001$). Ongoing randomized trials are addressing the issue of whether local drug delivery will reduce the CI-AKI rates in patients undergoing exposure to contrast media.

(l) Future preventive approaches

Many more approaches e.g. coronary sinus withdrawal of blood after intracoronary injection and thereby reducing the volume of contrast delivered downstream to the kidneys; or development of non-toxic imaging agents are being actively pursued.

Novel Biomarkers for Renal Dysfunction.

(i) Leipocalin is readily excreted and detected in urine due to its small size and since it is highly accumulated in human kidney, it may serve as a troponin for renal ischemic injury.

(ii) Cystatin-C is a serum protein filtered out of blood by kidneys and serves as an estimate of GFR irrespective of wt, height, muscle mass, age and gender.

(D) General recommendations

Non-steroidal antiinflammatory drugs and diuretics should be stopped 24 h before the procedure and can be reintroduced 24 h thereafter. Metformin should be discontinued on the morning of the procedure and restarted if CI-AKI has not developed. If serum creatinine has risen after a procedure, the next procedure should be delayed until serum creatinine has peaked and stabilized or, ideally, has returned to baseline. After the contrast study, serum creatinine levels should be followed for 24–48 h in medium-risk or high-risk patients.

(i) **Low-risk group**

All patients undergoing a contrast procedure should be instructed to drink at least 500ml water or soft drinks before the procedure and 2500 ml for 24 h after the procedure, or even more in warm areas.[174] When patients are required to remain fasting, we recommend the administration of 0.9% saline at a rate of 1 ml/kg body weight per hour (maximum 100 ml/h) starting 4 h before contrast administration and continuing for 24 h afterwards.

(ii) **Medium-risk group**

In patients with dehydration, circulatory collapse or congestive heart failure, the procedure should be delayed pending correction of the hemodynamic status. Intravenous hydration with 0.9% NaCl during 24 h starting 12 h before or on the morning of the procedure at a rate of 1 ml/kg body weight per hour is the gold standard. In patients at risk for fluid overload, the use of 0.45% saline is preferable. If intravenous hydration for at least 6 h before the procedure is not feasible,[115] the combination of oral hydration and intravenous fluid administration at a high infusion rate (3 ml/kg body weight per hour with a maximum of 300 ml/h)[109,116] starting 1 h before contrast exposure is advised and intravenous hydration should be continued at the usual rate of 1 ml/kg body weight per hour for at least 12 h after the procedure. The operator should keep the amount of dye as low as possible and use low-osmolar or iso-osmolar contrast medium. Although controversial, the use of 1200 mg acetylcysteine twice daily on the day of contrast procedure and the day before can be defended. For emergency procedures, an intravenous bolus of 1200 mg can replace the first oral dose.

(iii) **High-risk group**

Nephrological advice before the contrast procedure is desirable. A hydration protocol is mandatory, but often there will be a subtle balance between the protection of the renal function and avoidance of fluid overload, requiring an individualized protocol. Further, all other measures for the medium-risk group should also be applied here. In patients unable to receive appropriate hydration and/or admitted to the ICU, the administration of 200 mg theophylline 30 min before the procedure can be defended.

*Do not measure the baseline serum creatinine (SCr) concentration after administration of N-acetylcysteine (NAC); do not cancel or delay the procedure if NAC is not administered. (Adapted from Goldberg et al Mayo Clinic Proc (2): 170-79 2009)

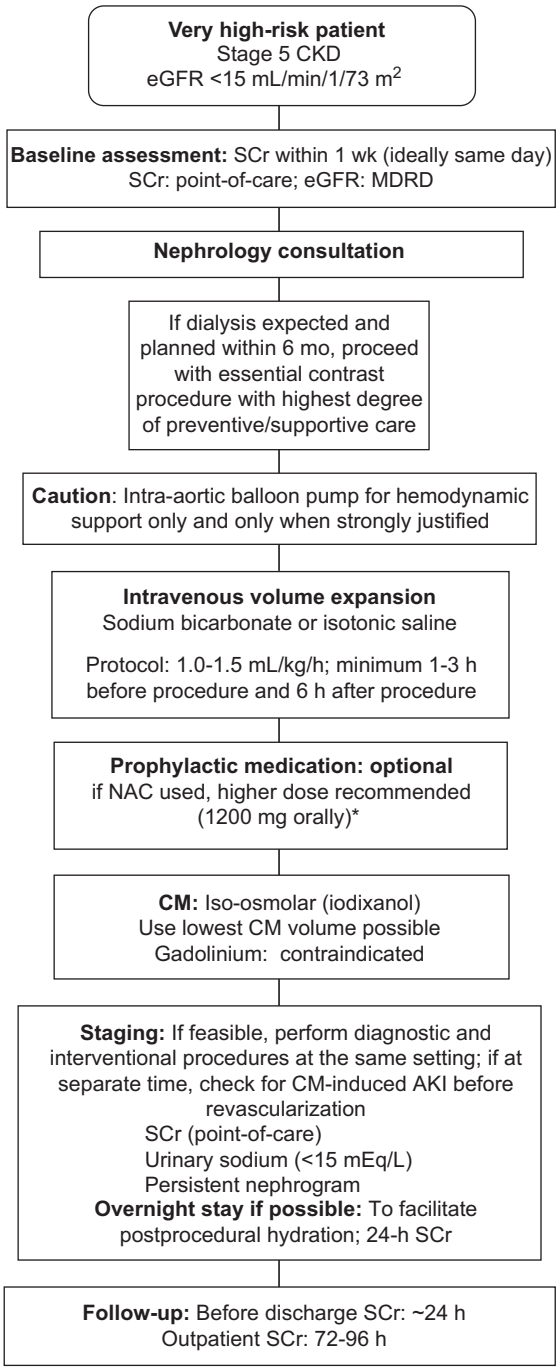


Figure 7 – Protocol for interventional cardiology

Follow up Procedure:. Class I:

Rpt S. creatinine 72 hrs later for eGFR < 59 ml/hr (Level of Evidence B)

Table 16 – Promising AKI Biomarkers: Current Status

	Cardiac Surgery	*Contrast*	*Sepsis/ICU*	*Kidney Transpl.*	*Comm. Test?*
NGAL (early)	Plasma Urine	Plasma Urine	Plasma Urine	Plasma Urine	Biosite[a] Abbott[a]
Cyst C (intermed)	Plasma	Plasma	Plasma	Plasma	Dade-Behring
IL-18 (intermed)	Urine	No	Urine	Urine	Nones
KIM-1 (intermed)	Urine	?	?	?	None

a In Development

Miscellaneous conditions

1. *Remote ischemic preconditioning*. The underlying mechanism for CI-AKI has been attributed in part to ischemic kidney injury. Remote ischemic preconditioning (IPC) may offer a novel, non-pharmacological prevention strategy for decreasing CI-AKI incidence in patients undergoing angiography. It is assumed that IPC confers protective effects on tissue or organ by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ. This has been proved in the recent Randomized Pilot RenPro Trial.[175] It is however,still investigational.

2. *New AKI markers*. Potentially effective preventive and therapeutic measures are frequently delayed due to lack of early diagnostic markers of AKI. Current markers rise after function is already lost and window of benefit from intervention closed or closing.[176] Emerging technologies are yielding novel, early, non-invasive biomarkers for the prediction of AKI as outlined in the table below (Table 16–18).

3. *Timing of cardiac surgery post angiography*. Recently, there has been an interest in the temporal relationship between coronary angiography and cardiac surgery suggesting that a 'double hit' on the renal function in close succession increases the risk of AKI after cardiac surgery.[177–180]

There have been a few relatively small studies on the association between the risk of post-operative AKI and the timing of contrast exposure before the cardiac surgery, but the results are mixed.[177–180]

However In the most recent and largest retrospective cohort study till date[181,182] ($N > 2000$), it was found that the number of days between coronary angiogram and cardiac surgery was not a predictor of post-operative AKI. These results remained the same in high-risk subgroups such as the patients with pre-operative renal insufficiency or those who had CI-AKI. The independent predictors of AKI after cardiac surgery in this cohort were advanced age, high body mass index, diabetes mellitus, NYHA class III/IV, prolonged cardiopulmonary bypass time, and impaired pre-operative renal function (eGFR < 60 mL/min/1.73 m^2).Hence at this time there appears to be no effect .

4. *ACE/ARB during coronary angiography*. CI-AKI is associated with increased morbidity and mortality in patients undergoing diagnostic procedures and/or interventional procedures in the cardiac catheterization laboratory Because many patients who are referred for cardiac catheterization have comorbidities for which ACEIs are utilized, the precise role of these medications in the pathogenesis of CI-AKI needs to be clarified. There have been studies that report a protective effect,[183] studies that report a negative effect,[184,185] and studies that report no effect.[186] However, virtually all clinical studies are relatively small studies and most of them are retrospective and further studies are warranted to define the role of the ACEIs in CI-AKI.

Table 17 – 6.ESC 2010 GUIDELINES FOR THE PREVENTION OF CI-AKI[188]

Intervention	Dose	Class[a]	Level[b]
All patients with CKD			
OMT (including stains, β – blockers, and ACE inhibitors or sartans) is recommended	According to clinical indications	I	A
Hydration with isotonic saline is recommended	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 ml/kg/h if EF $< 35\%$ OR NYHA > 2).	I	A
N-acetylcysteine administration may be considered	600–1200 mg 24 h before and continued for 24 h after the procedure	IIb	A
Infusion of sodium bicarbonate 0.84% may be considered	1 h before: bolus = body weight in kg $\times$ 0.462 mEq i.v. infusion for 6 h after the procedure = body weight in kg $\times$ 0.154 mEq/hour.	IIb	A
Patients with mild, moderate, or severe CKD			
Use of LOCM or IOCM is recommended	<350 mL or <4 mL/kg	I[d]	A[d]
Patients with severe CKD			
Prophylactic hemofiltration 6 h before complex PCI should be considered.	Fluid replacement rate 1000 mL/h without weight loss and saline hydration, continued for 24 h after the procedure.	IIa	B
Elective hemodialysis is not recommended as a preventive measure		III	B

Table 18 – ACC 2011 GUIDELINES FOR THE PREVENTION OF CI-AKI[189]

Recommendations	COR	LOE
Contrast-induced AKI		
Patients should be assessed for risk of contrast- induced AKI before PCI	I	C
Patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration.	I	B
In patients with CKD (creatinine clearance <60 mL/min), the volume of contrast media should be minimized.	I	B
Administration of N-acetyl-L-cysteine is not useful for the prevention of contrast-induced AKI	III: No Benefit	C

Based on the data, there is no definite correlation between ACEIs and the occurrence of CI-AKI postcontrast exposure. Even when evaluating specific subgroups, such as those with chronic kidney disease, the data are not consistent and a definitive correlation between ACEIs and CI-AKI cannot be established. Thus, withholding ACEIs prior to catheterization does not probably decrease the incidence of CI-AKI and is not recommended. By the same token, starting ACEIs before the procedure for the sole purpose of lowering the risk of CI-AKI cannot be recommended based on the current evidence.

5. *Metformin stoppage during coronary angiography*. Concerns about metformin-associated lactic acidosis (M-ALA) in patients undergoing contrast-based angiographic procedures have led to the development and publication of a number of guidelines to improve the management of this patient cohort. However, the evidence for M-ALA in diabetics on metformin undergoing coronary intervention is lacking and existing guidance on the management of such patients is inconsistent.[187] More robust evidence is needed in the form of a large, adequately-sized randomized trial or extensive registry so that we can optimally manage those patients requiring contrast-based coronary interventions who are also taking metformin.

Conclusion

The Working group on development of Guidelines for angiography in renal dysfunction looked at all the relevant literature till June 2010 and this was subsequently updated till Oct 2012. This is presented in both ACC/AHA as well as the tabular ESH format. The ESH recently published Guidelines of Angiography in CKD as a part of guidelines for PCI/CABG in Coronary Artery Disease. This included only guidelines for prevention of CKD. The current CSI Guidelines are more broad based and have included risk calculation, prevention as well as post care of these patients.

These guidelines should form an important resource for the busy practitioners, interventionists and nephrologists who care for patients with CKD and thus enable them to provide for a safe angiography/PCI in this setting.

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