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REVIEW TOPIC OF THE WEEK

Contrast-Induced Acute Kidney Injury

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ABSTRACT

Coronary angiography and percutaneous intervention rely on the use of iodinated intravascular contrast for vessel and chamber imaging. Despite advancements in imaging and interventional techniques, iodinated contrast continues to pose a risk of contrast-induced acute kidney injury (CI-AKI) for a subgroup of patients at risk for this complication. There has been a consistent and graded signal of risk for associated outcomes including need for renal replacement therapy, rehospitalization, and death, according to the incidence and severity of CI-AKI. This paper reviews the epidemiology, pathophysiology, prognosis, and management of CI-AKI as it applies to the cardiac catheterization laboratory.
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There have been many advancements in the field of interventional cardiology that have resulted in a greater degree of patient safety and have allowed an ever-increasing population at risk to undergo diagnostic and interventional procedures. Despite these steps forward, accurate imaging of the coronary and peripheral vasculature remains dependent on the use of intravascular injection of iodinated contrast, which has well-known toxicities, including contrast-induced acute kidney injury (CI-AKI). This paper presents an update on the epidemiology, pathogenesis, prognosis, and management of CI-AKI as applied specifically to cardiac interventional procedures.

EPIDEMIOLOGY

There are considerable sources of information indicating that CI-AKI, and perhaps AKI overall, in patients undergoing cardiac catheterization procedures has been declining over the past decade or more. However, among those undergoing cardiac surgery after coronary angiography, AKI and AKI requiring dialysis (AKI-D) may be increasing. In 2012, Amin et al. (1) reported on 33,249 hospitalizations for acute myocardial infarction in the United States of 31,532 patients and demonstrated that the rate of AKI declined from 26.6% in 2000 to 19.7% in 2008 (26% reduction) using a definition consistent with the Kidney Disease International Global Outcomes Guidelines of a rise in serum creatinine (sCr) ≥0.3 mg/dl or a ≥50% elevation from baseline over the course of hospitalization. The National Cardiovascular Data Registry Cath-PCI (N = 985,737 who underwent elective and urgent percutaneous coronary intervention [PCI]) reported 69,658 (7.1%) cases of CI-AKI (sCr rise ≥0.3 mg/dl) and 3,005 (0.3%) cases of AKI-D (Figure 1) (2). Although in Figure 1, estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 is indicated to be normal, it may not be the case if it is in the setting of a unilateral kidney or in a patient with structural kidney disease (e.g., polycystic kidney disease). As chronic kidney disease (CKD) progresses and eGFR worsens, there is a sharp increase in the rates of both CI-AKI and AKI-D, as shown in Figure 1. The most important factors associated with a more than doubling in the rates of CI-AKI and significant increases in the risk of AKI-D were ST-segment elevation myocardial infarction (STEMI), eGFR <30 ml/min/1.73 m^2, and cardiogenic shock. Mean

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-enzyme inhibitor

ACS = acute coronary syndromes

AKI-D = acute kidney injury requiring dialysis

ARB = angiotensin-receptor blocker

CI = confidence interval

CI-AKI = contrast-induced acute kidney injury

CKD = chronic kidney disease

Cr = creatinine

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

HF = heart failure

HR = hazard ratio

LVEDP = left ventricular end-diastolic pressure

MI = myocardial infarction

PCI = percutaneous coronary intervention

RASi = renin-angiotensin system inhibitors

sCr = serum creatinine

STEMI = ST-segment elevation myocardial infarction

TAVR = transcatheter aortic valve replacement

contrast volumes among those with CI-AKI ranged from 140 to 260 ml, similar to those without CI-AKI (140 to 245 ml). Thus, although rates of CI-AKI may have historically trended down over the past decade, the risk is still formidable in the patients with the greatest need for urgent PCI, including those with STEMI and those developing cardiogenic shock. In addition, the overall age in this report from the Cath-PCI registry is 64.8 ± 12.2 years and thus is not reflective of the growing numbers of the elderly undergoing PCI currently and in the future. As the Cath-PCI registry report elucidated, baseline eGFR, STEMI, and cardiogenic shock are strong predictors of CI-AKI and AKI-D after PCI. Mehran et al. (3) developed and validated a comprehensive risk prediction score, which also included age, hemoglobin, pre-existing CKD, contrast volume, need for intra-aortic balloon counterpulsation, and other variables, in order to anticipate the rate of CI-AKI, as well as the need for renal replacement therapy. Although this tool can be used for quality reporting and other functions, it is not helpful before the procedure because it incorporates variables that can only be known after the case is completed in the catheterization laboratory. For pre-procedural counseling, the most useful parameters are the eGFR and presence of diabetes. In general, eGFR <60 ml/min/1.73 m^2 with diabetes elevates the risk of CI-AKI sufficiently above the baseline of ~5% to ~10%; thus, appropriate counseling and preventive measures are warranted to mitigate this potential adverse consequence of angiography.

PATHOPHYSIOLOGY

All forms of iodinated contrast are highly water-soluble carbon-based benzene rings that exist as monomers with 3 iodine atoms attached or as dimers with 6 iodine atoms attached. The most common types of contrast agents used today for intravascular injection are either iso-osmolar (approximately 290 mOsm/kg) iodixanol, which is a dimer, or low-osmolar (700 to 850 mOsm/kg) nonionic monomers (iohexol, iomeprol, iopamidol, iopromide, ioversol, ioxilan) (4). High-osmolar contrast agents (1,200 mOsm/kg or higher) are no longer used for cardiac catheterization. The iodine concentration of these products is similar (320 to 270 mg I/ml). However, when administered in the blood at 37°C, the 11.8 centipoise (cps) viscosity of iodixanol is significantly higher than that of iohexol, at 6.3 cps, the lowest in the low-osmolar category. In a rat model, the viscosity in urine can be considerably greater with iodixanol (5). Among these 3 physiochemical properties, the higher the osmolality or the particle concentration in solution, the greater the vascular symptoms of warmth and pain during injection, as well as CI-AKI (6). When iodinated contrast is injected into the systemic arterial circuit, there is a transient endothelium-dependent vasodilation mediated by release of nitric oxide, followed by arteriolar vasoconstriction lasting for several seconds to minutes in the peripheral circulation (**Figure 2**) (7). In the renal arcade of blood vessels that subdivide into the afferent glomerular arteriole serving the glomerulus, efferent arteriole dividing and forming the peritubular network, and finally the vasa recta, the transient dilation can be followed by a period of sustained vasoconstriction that lasts for several hours (7). When there is a reduced renal parenchymal mass and fewer nephrons in the setting of CKD and among those with diabetes, the reduction in renal blood flow can be sufficiently sustained to impair oxygenation to the outer medulla, resulting in ischemia to the proximal and distal tubules. Furthermore, the water-soluble contrast is readily taken up by the apical surface of proximal tubular cells (pumps, bystander endocytosis) and out of the basal-lateral surface into the tubulointerstitial space (8). Tubular cells undergo swelling, blebbing, and apoptosis, as shown in **Figure 2**. As a result, there is stasis of contrast within the kidneys after the procedure is completed. Of note, 3-hydroxy-3-methyl-glutaryl-CoA reductase regulates the production of isoprenoid pyrophosphates, which in turn play a key role in the proper function of guanosine triphosphate-binding protein-mediated endocytosis (9). In an in vitro model, statins inhibit endocytosis in renal tubular cells (10). This is the putative, beneficial mechanism of action attributed to statins, which will be discussed later. With high concentrations of contrast within and surrounding renal tubular cells, there is direct cellular toxicity with loss of the tubular brush border, breakdown of desmosomes, loss of cell membrane integrity, and sloughing of material into the urinary tubular space (Tamm-Horshfall protein), which promotes further stasis of contrast in the urine, enabling more movement of contrast into the tubulointerstitial space, where there is no ready form of clearance. Patients with CKD and diabetes have been reported to have persistent nephrograms where contrast can be seen within the kidneys for up to 8 days after contrast administration (11). The

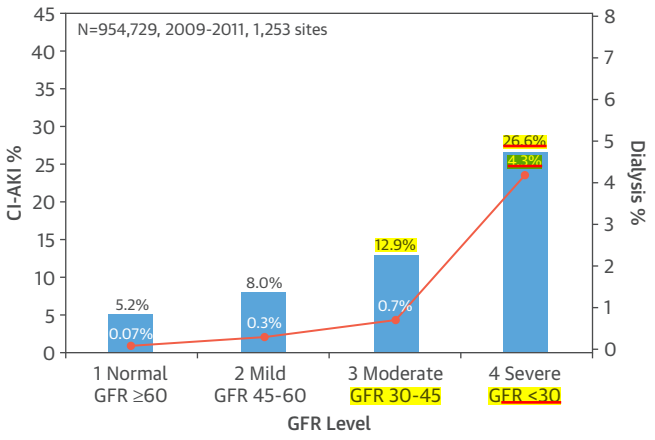
combination of both ischemic and chemotoxic injury to the proximal tubules triggers a process called tubuloglomerular feedback, which signals the glomerulus to reduce filtration, and hence the rise in the plasma concentration of creatinine (Cr) is seen approximately 24 to 48 h after there has been a significant reduction in filtration (12). Newly available urine markers of tubular damage (**Figure 3**) can elevate within a few hours of tubular injury (neutrophil gelatinase-associated lipocalin, fatty-acid binding protein, and cell-cycle arrest markers [insulin-like growth factor binding protein-7, tissue inhibitor of metalloproteinase-2]) (13). These markers hold promise for the detection of subclinical CI-AKI, as well as early detection of more severe cases, where future treatments may be applied before there is cessation of renal filtration and a drop in urine output.

Iodinated contrast does not injure the glomerulus; therefore, no hematuria is seen. Contrast is water soluble and freely filtered; however, its water solubility allows relatively easy reabsorption by the proximal tubular cells, where it causes cellular damage (8). Recent evidence suggest that as renal tubular cells are damaged, the mitochondria release intracellular catalytic or unbound iron, which serves as the catalyst in the Haber-Weiss and Fenton equations to drive oxidative stress and the production of the dangerous hydroxyl radical (14). A similar process is accentuated by exposure of iron-rich myoglobin in the setting of rhabdomyolysis, as well as heme in the setting of cardiac surgery (15). Of interest, the 3 ways of reducing these oxidative stress reactions are: 1) reduce temperature (as is done during cardiac surgery); 2) alkalinize the environment; or 3) remove the substrate and or catalyst (14). Additionally, alkalinization reduces the precipitation of Tamm-Horsfall protein in the tubular lumen (16).

Subclinical CI-AKI may occur in every patient exposed to iodinated contrast. Because there is a robust tubular repair capability in healthy subjects, this process may not have any clinical consequences (17). However, in patients with CKD and diabetes mellitus, who have a reduced number of functioning nephrons and an impaired ability to regenerate tubular epithelial cells, routine cardiac procedures using average doses of iodinated contrast can cause CI-AKI that is clinically important. The natural history of acute tubular injury follows a time course of approximately 8 to 10 days, with recovery and regeneration of tubular cells from within the tubule structure. However, with each exposure of contrast, there may be sufficient destruction to some nephrons that recovery is not possible, and ultimately, there is loss of the functional unit, replaced by fibrosis. Thus, in those with few functioning nephron units and advanced CKD (eGFR <30 ml/min/1.73 m^2), CI-AKI can result in such a relatively large proportional reduction in renal filtration to yield azotemia, volume overload, and hyperkalemia warranting renal replacement therapy. In approximately one-half of these cases, there is permanent end-stage renal disease (ESRD), whereas in the other one-half, there can be eventual recovery that allows some period of dialysis-free survival.

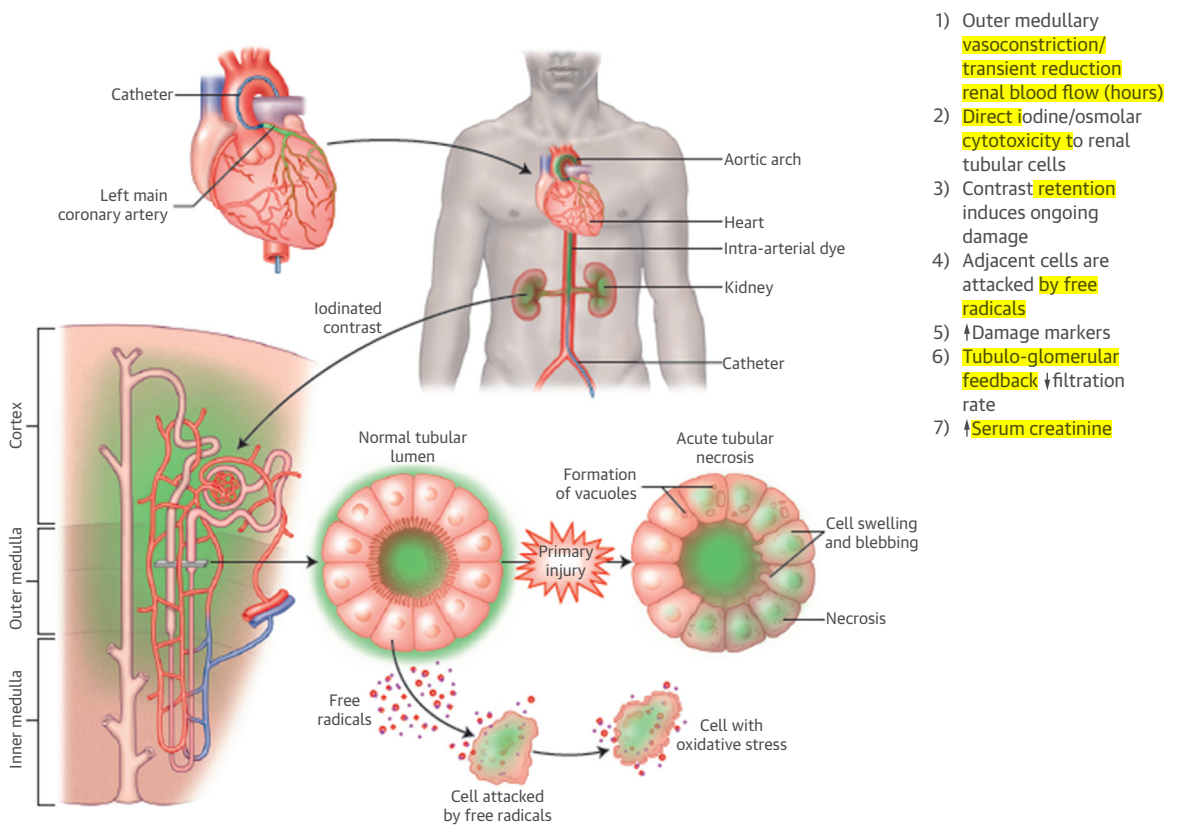
With catheter administration of intra-arterial contrast, there is the opportunity for microshowers of atheroembolic material to the renal and systemic circulation. Because the kidneys receive 25% of cardiac output, it has been hypothesized that microembolism not detected clinically accounts for some portion of CI-AKI. The relative contribution of renal atheroemboli may be greater in CI-AKI cases after transcatheter aortic valve replacement (TAVR), where the proportion of cases that result in severe acute kidney injury appears to be higher than in reports from PCI registries. However, a pooled analysis has suggested that TAVR is associated with a lower risk of AKI compared with surgical valve replacement (18). In studies of patients with similar levels of renal function and contrast doses given in the venous system, there are consistently lower rates of CI-AKI, largely because there is no opportunity for atheroembolism and possibly because of a greater admixture of contrast in the blood pool before the kidneys are

FIGURE 1 Incidence of CI-AKI and New ESRD Requiring Dialysis From the ACC Cath-PCI Registry



Incidence of CI-AKI and new ESRD after coronary angiography with PCI according to baseline renal filtration function. Adapted with permission from Tsai et al. (2). ACC = American College of Cardiology; CI-AKI = contrast-induced acute kidney injury; ESRD = end-stage renal disease; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention.

FIGURE 2 Pathogenesis of CI-AKI



This figure demonstrates that from the point of injection into the coronary arteries, iodinated contrast triggers a series of hemodynamic responses and direct cellular injury as it reaches the kidneys. Adapted with permission from Brown and McCullough (33). CI-AKI = contrast-induced acute kidney injury.

exposed. Additionally, acute coronary syndrome (ACS) and, in particular, STEMI patients have been observed to have nearly double the rates of CI-AKI. This may be due to neurohormonal activation, release of catalytic iron from the heart, inadequate opportunity for volume expansion, and greater rates of hemodynamic instability.

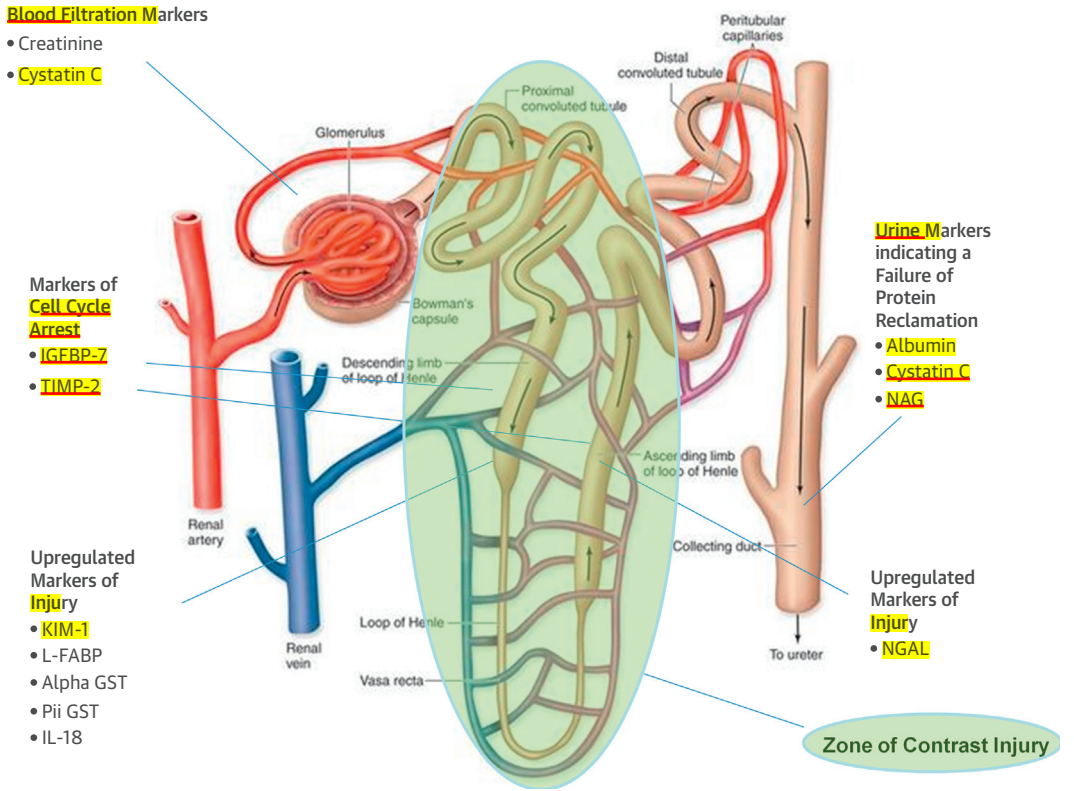
PROGNOSIS

Studies have consistently reported higher rates of virtually every complication after PCI in those who experience CI-AKI. Direct complications of CI-AKI can include volume overload and hyperkalemia that require urgent dialysis, the development of ESRD, and death. However, CI-AKI is a clinical marker for individuals who are more frail, and susceptible to medical and procedural complications. In the report from the Cath-PCI registry, the rates of recurrent myocardial infarction (MI), major bleeding (≥3 g/dl decrease in hemoglobin, transfusion of whole packed red blood cells, or an intervention to stop the bleeding within 72 h of the procedure), and death in those not on dialysis, and with no evidence of CI-AKI after contrast administration were 2.1% MI, 1.4% bleeding, 0.5% death. These outcomes were all significantly higher in those with CI-AKI (3.8% MI, 6.4% bleeding, 9.7% death) and considerably greater in those with AKI-D (7.9% MI, 15.8% bleeding, 34.3% death). Although confounding by known variables, such as older age, female sex, diabetes, severity of coronary disease, left ventricular dysfunction, presentation as non-STEMI, STEMI, cardiogenic shock, or cardiac arrest are the most likely explanation for these higher rates of events, it is possible that acute tubular injury triggers clinical events in other organs on the basis of yet-to-be understood mechanisms.

MANAGEMENT

Principles of management include using volumes of contrast that are as low as reasonably achievable

FIGURE 3 Anatomy of a Single Nephron and Location of Novel and Conventional Biomarkers of Renal Filtration and Tubular Epithelial Cell Damage

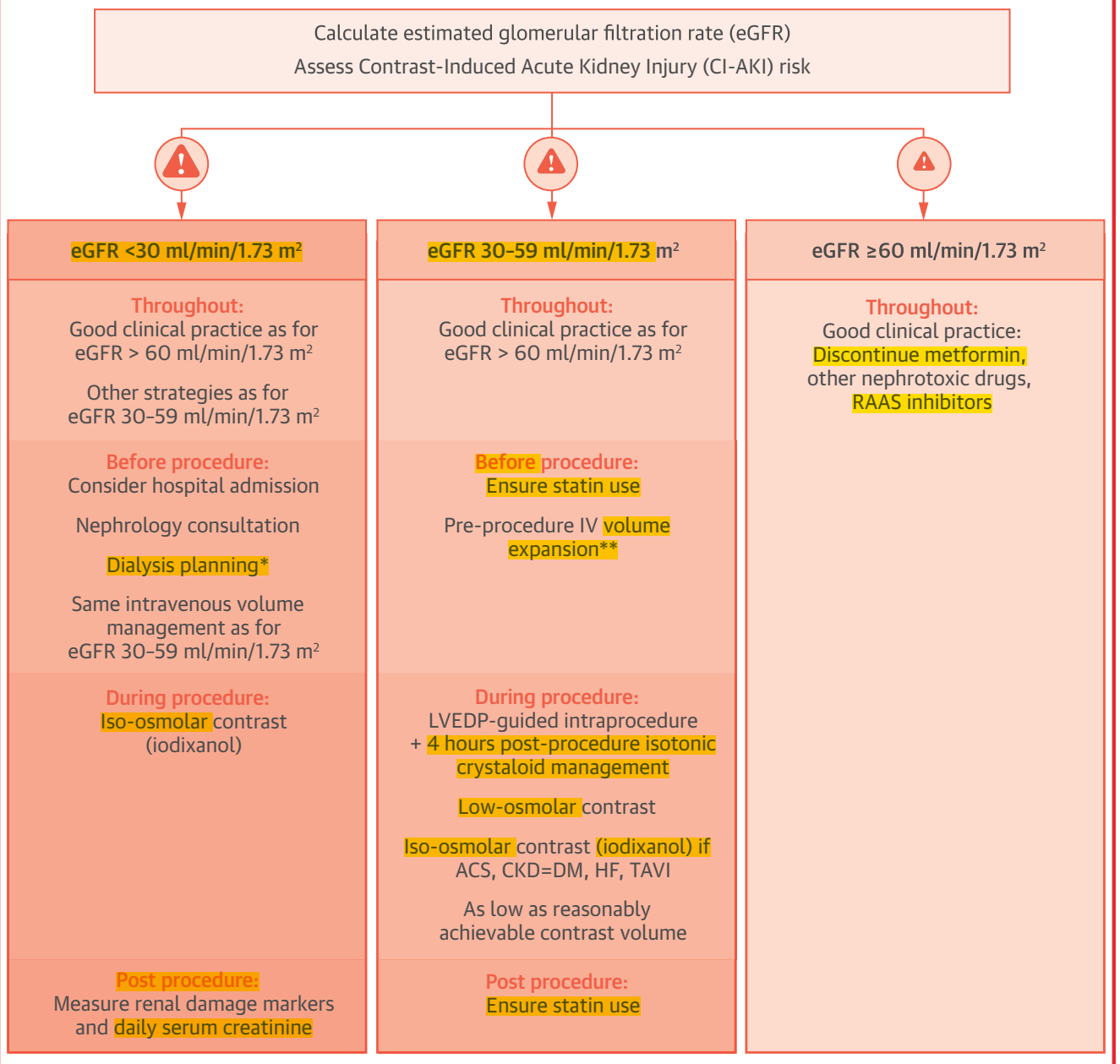


Markers of filtration indicate transient reductions in glomerular function, whereas cell damage markers indicate cellular injury, and the 2 together have a poorer prognosis than either alone. Not all of these markers have been validated for CI-AKI. Cell cycle arrest markers are TIMP2*IGFBP-7 (tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7). CI-AKI = contrast-induced acute kidney injury; GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty-acid binding protein; NAG = *N*-acetyl-beta-D-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin.

(ALARA) and selection of the least-toxic iodinated contrast agent in the highest-risk patients (**Central Illustration**). Low-osmolar contrast agents are reasonable for moderate-risk patients and iso-osmolar contrast is indicated for the highest-risk patients. In patients with high-risk profiles (eGFR <30 ml/min/1.73 m^2 with diabetes, heart failure [HF], or urgent PCI for ACS), there is no absolutely safe limit of contrast dose; hence, the most reasonable approach is to maximize the benefit to risk balance of the procedure by performing revascularization and then expectantly manage the CI-AKI to follow. Contrast minimization can be achieved using in-line devices in the contrast tubing manifold system that work to reduce injection overshoot by the operator (AVERT Plus System, Osprey Medical, Minnetonka, Minnesota). This system is currently being tested against expert operators in an attempt to reduce the incidence of CI-AKI (19). Avoiding left ventriculography and aortography are additional strategies commonly used to reduce the overall contrast dose.

Because iodinated contrast is water soluble, it is amenable to prevention strategies that expand intravascular volume and increase renal filtration and tubular flow of urine into collecting ducts, and on into the ureters and bladder. CI-AKI is responsive to intravascular administration of isotonic crystalloid solutions to enhance renal elimination of contrast via the urine. There have been numerous randomized trials comparing isotonic bicarbonate solutions to intravenous saline, and in the largest and highest-quality trials, there have been no differences in the rates of renal outcomes (20,21). Hence, either isotonic crystalloid solution is recommended, with some guidance on the quantity of fluid according to patient factors. The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial

CENTRAL ILLUSTRATION **Algorithm for the Prevention and Management of CI-AKI**



McCullough, P.A. et al. J Am Coll Cardiol. 2016;68(13):1465–73.

*Plans should be made in case CI-AKI occurs and dialysis is required. **IV isotonic crystalloid 3 ml/kg/h for 1 h before. Initial LVEDP-guided crystalloid: <13 mm Hg → 5 ml/kg/h × 4 h; 13 to 18 mm Hg → 3 ml/kg/h × 4 h; >18 mm Hg → 1.5 ml/kg/h × 4 h. Renal damage markers: IGFBP-7*TIMP2 (NephroCheck), NGAL, L-FABP. ACS = acute coronary syndromes; CI-AKI = contrast-induced acute kidney injury; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure; IGFBP-7*TIMP2 = insulin-like growth factor binding protein-7 concentration multiplied by tissue inhibitor of metalloproteinase-2 concentration; IV = intravenous; L-FABP = L-type fatty-acid binding protein; LVEDP = left ventricular end-diastolic pressure; NGAL = neutrophil-associated lipocalin; RAAS = renin-angiotensin-aldosterone system; TAVI = transcatheter aortic valve implantation.

randomized 396 patients with eGFR <60 ml/min/1.73 m^2 and 1 additional risk factor to a strategy of measurement of left ventricular end-diastolic pressure (LVEDP) and expanding plasma volume versus usual care. Each group had standard-of-care of normal saline 3 ml/kg for 1 h before cardiac catheterization. The LVEDP-guided approach (**Central Illustration**) was associated with more intensive fluid administration during and after the procedure, and was associated with a reduction in CI-AKI (6.7% [12 of 178]) compared with the control group (16.3% [28 of 172]; relative risk: 0.41, 95% confidence interval [CI]: 0.22 to 0.79; p = 0.005). Intravenous fluid was terminated prematurely because of concerns regarding volume overload in only 3 patients in each group. Even more intensive management with intravenous crystalloid with forced diuresis has been tested in a series of randomized trials using a fluid balance system that measures and controls intravenous crystalloid volume with urine output (RenalGuard System, PLC Medical Systems, Milford, Massachusetts). All of these trials have demonstrated that elevation of urine output to >150 ml/h before and during the procedure reduces rates of CI-AKI (22). In a single-center trial, 112 consecutive patients undergoing TAVR were randomly assigned to normal saline controlled by the RenalGuard system with urine flow initially augmented by furosemide (RenalGuard group) or normal saline-based usual care (control group). The primary endpoint was the incidence of CI-AKI (Cr rise ≥0.3 mg/dl or ≥50%) in the first 72 h after the procedure. The AKI rate was lower in the RenalGuard group than in the control group (n = 3 [5.4%] vs. n = 14 [25.0%], respectively; p = 0.014). No case of in-hospital AKI-D was reported. No significant differences in terms of mortality, cerebrovascular events, bleeding, and hospitalization for HF were noted in either group at 30 days.

To date, no adjunctive pharmaceutical has been demonstrated to effectively prevent or treat CI-AKI. There has been a pattern of small, randomized trials and meta-analyses of these trials showing benefit with a specific agent (e.g., *N*-acetylcysteine, ascorbic acid, aminophylline, trimetazidine, fenoldopam, among others), often with low event differences between the groups and large effect sizes attributable to alpha error or imbalanced randomization (23,24). When subjected to large randomized clinical trials, every agent tested to date has failed to prevent and/or treat CI-AKI. Thus, large clinical trials have an important role in this field. *N*-acetylcysteine is currently being tested in a randomized factorial design with sodium bicarbonate in a large (N = 8,680) definitive trial (PRESERVE [Prevention of Serious Adverse Events Following Angiography]) (25). At the present time, however, 2 chronic therapies may have an influence on CI-AKI, despite being used for other reasons, statins and renin-angiotensin system inhibitors (RASi): angiotensin-converting enzyme inhibitors [ACEI] and angiotensin-receptor blockers [ARB]).

Statins appear in all observational and randomized studies to date to protect against the development of CI-AKI. Statins may be renoprotective via several mechanisms, including inhibition of uptake of contrast into renal tubular cells, attenuation of endothelial dysfunction and oxidative stress, anti-inflammation, antiproliferation of mesangial cells, and protection of podocytes. In 2012, Li et al. (26) performed a meta-analysis that again looked at the benefit of short-term high-dose statins in the prevention of CI-AKI, which included 7 studies and 1,399 patients. They found a significant improvement in the incidence of CI-AKI, but no benefit in AKI-D. The PRATO-ACS (Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome) trial analyzed the role of rosuvastatin in statin-naïve patients for preventing CI-AKI (27). They randomized 504 statin-naive non-STEMI ACS patients undergoing PCI to statin or no statin therapy. Statin patients received rosuvastatin 40 mg on admission, then 20 mg daily, whereas the control patients did not receive statins during the hospitalization. At discharge, the statin group continued treatment with 20 mg/day rosuvastatin (10 mg/day for patients with GFR <30 ml/min/m^2), whereas controls received 40 mg/day atorvastatin. CI-AKI was defined as a rise in sCr by 0.5 ml/dl or 25% above baseline within 72 h of receiving contrast. The study found the statin group had a significantly lower rate of CI-AKI than the no statin group (6.7% vs. 15.1%; adjusted odds ratio: 0.38; 95% CI: 0.20 to 0.71; p = 0.003). This benefit was significant across all pre-specified risk categories. In addition to the primary endpoint, multiple positive secondary endpoints were noted. There was a decrease in 30-day composite death, dialysis, MI, stroke, or persistent renal damage in the statin group (3.6% vs. 7.9%, respectively; p = 0.036), as well as a trend toward a decrease in death or MI at 6 months (3.6% vs. 7.2%, respectively; p = 0.07). Han et al. (28) tested rosuvastatin in prevention of CI-AKI in 2,998 patients with diabetes and CKD who were undergoing coronary or peripheral angiography with or without intervention. Patients who were on statins previously were asked to hold their statin for 14 days before the procedure. Patients were randomized to statin therapy or standard of care (no statin). The statin group

received rosuvastatin 10 mg daily starting 2 days before the procedure and continuing for 5 days. The standard of care group and statin group resumed statin therapy 3 days after intervention. CI-AKI was defined as an increase of sCr concentration ≥0.5 mg/dl or 25% above baseline at 72 h. The statin group had a significantly lower incidence of CI-AKI (2.3% vs. 3.9%; p = 0.01). Additionally, a significantly lower rate of HF was noted in the statin group at the 30-day follow-up (2.6% vs. 4.3%; p = 0.02) (28).

RASi are proven therapies for hypertension and HF, and are indicated to reduce the progression of diabetic nephropathy. The chronic beneficial effect of RASi on the kidney is mediated, in part, by reduction of intraglomerular pressure due to efferent glomerular arteriolar dilation. This mechanism, however, may be deleterious to the kidneys in the setting of acute illness or in the setting of iodinated contrast, where the ability to raise intraglomerular pressure/filtration via tubuloglomerular feedback may be beneficial in maintaining glomerular filtration and forward flow of urine through the proximal tubules and the remainder of the nephron. The most recent trial to address this issue was the CAPTAIN (Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization) trial, which randomly assigned 208 patients with Cr ≥1.7 mg/dl within 3 months or ≥1.5 mg/dl within 1 week before coronary angiography to hold RASi (ACEI 72.1% or ARB 27.9%) ≥24 h pre-procedure or continue RASi. The primary outcome was the incidence of CI-AKI, defined as an absolute rise in sCr ≥0.5 mg/dl from baseline and/or a relative rise in sCr ≥25%. At 48 to 96 h, CI-AKI occurred in 10.9% of RASi-held compared to 18.4% of RASi-continued patients (hazard ratio [HR]: 0.59; 95% CI: 0.30 to 1.19; p = 0.16). In a pre-specified secondary outcome, there was a lower rise in mean sCr after the procedure in patients who held ACEI/ARB (0.3 ± 0.5 mg/dl vs. 0.1 ± 0.3 mg/dl; p = 0.03). A clinical composite of death, MI, ischemic stroke, congestive HF, rehospitalization for cardiovascular cause, or need for dialysis periprocedural occurred in none of the RASi-held and 3.9% of the RASi-continued groups (HR: 0.11; 95% CI: 0.01 to 2.96; p = 0.06). These data, combined with reports from CKD trials, suggest that although RASi are beneficial chronically, either too intensive RASi (ACEI + ARB) or direct renin inhibition appears to have excessive toxicity in the setting of hospitalization, and probably in the setting of cardiac catheterization and PCI as well (29,30). Thus, it appears to be reasonable to hold RASi before coronary angiography in moderate and above-risk patients.

FUTURE DIRECTIONS

It appears that we are considerably invested in fluoroscopy and cineangiography in the world of invasive cardiology for many years to come. Technology to minimize contrast by avoiding over-injection and accurately recording contrast volumes will provide some help as our procedures become ever more complicated (31). This being considered, novel forms of nontoxic radio-opaque contrast would be welcomed; however, we are aware of no such new molecular entities in development. Attempts to render iodine-based radiocontrast less toxic are promising, particularly with the use of cyclodextrin, which makes contrast stay in the urinary space and less likely to penetrate the kidney tissue and cause damage (32). Finally, the development of cellular protectants continues to be an area of interest and, despite the disappointing results with n-acetyl cysteine, sodium bicarbonate, prostaglandins, fenoldopam, and other agents, there is hope that an adjunctive agent could be administered that would render the kidneys less susceptible to damage, and possibly protect the heart and other organs as well.

CONCLUSIONS

CI-AKI remains a concern for patients undergoing cardiac interventional procedures utilizing intravascular iodinated contrast. This form of renal injury appears to be amenable to volume expansion and to measures to increase urine flow and removal of highly water-soluble contrast. Minimizing contrast by use of ALARA principles and strategies to maximize the benefit of contrast exposure (i.e., revascularization) are reasonable. Although no adjunctive therapy is prophylactic or therapeutic for CI-AKI, statin use appears to reduce the incidence and severity of AKI, whereas continuation of RASi appears to increase the risk for CI-AKI. Further research is needed in the development of less toxic contrast agents, as well as therapies that can reduce cardiorenal complication of interventional cardiovascular procedures. Such agents hold the promise of improving long-term outcomes by minimizing the hazards of intercurrent events, such as ACS, and urgent and planned catheterization procedures.

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