Contrast-Induced Nephropathy

Julian L. Wichmann, MD; Richard W. Katzberg, MD; Sheldon E. Litwin, MD; Peter L. Zwerner, MD; Carlo N. De Cecco, MD, PhD; Thomas J. Vogl, MD; Philip Costello, MD; U. Joseph Schoepf, MD

Case Presentation

A 48-year-old man presents to the Emergency Department and complains of new onset of chest pain with exertion. He has a history of tobacco use, hypercholesterolemia, type 2 diabetes mellitus, and chronic renal disease (baseline serum creatinine concentration [SCr] 1.7 mg/dL; estimated glomerular function [eGFR] 47 mL/min per 1.73m^2). Initially, he undergoes coronary computed tomography (CT) angiography, which demonstrates >75% narrowing of the proximal left anterior descending coronary artery. The next day he undergoes coronary catheterization with successful drug-eluting stent placement to an 80% stenosis of the left anterior descending coronary artery. He receives a total of 211 mL contrast agent (320 mgI/mL; 67.52 g iodine) from both examinations. His SCr level increases to a peak of 2.4 mg/dL at 48 hours after percutaneous intervention, returning to baseline over the next 72 hours. He recovers uneventfully. The treating physicians diagnose him with postinterventional contrast-induced nephropathy (CIN).

After the introduction of iodinated contrast agents in the last century, their use was promptly linked to acute kidney injury (AKI).[1] The presumed causal relationship between contrast medium (CM) exposure and AKI has since been axiomatic in clinical care, with substantial implications for patient management in the context of contrast-enhanced imaging. Indeed, fear of contrast-induced AKI is one of the most frequent reasons why CM is withheld from patients and thus frequently compromises the diagnostic information gained from imaging. Despite the nearly universal concern about the risks of CIN, several recent large-scale studies have questioned the general concept of CIN and the relationship between CM administration, AKI, and worsened clinical outcome.[2,3] In fact, AKI may occur at similar rates in matched control groups of patients undergoing CT scanning with and without CM administration.[4,5] Therefore, a clear differentiation between AKI due to other causes and true CIN is crucial when discussing the potential side effects of CM administration with patients. In this Clinician Update, we summarize recent insights into AKI, CIN, and recommendations for management of patients receiving CM in clinical practice.

Definition

AKI is generally described as an acute worsening of renal function and referred to as CIN if it occurs within a narrow time interval after parenteral CM administration.[1] To standardize the definition for CIN, the Acute Kidney Injury Network[6] requires that, for a diagnosis of postcontrast AKI, at least 1 out of 3 conditions is met within 48 hours after contrast media application: (1) an absolute increase in SCr by ≥0.3 mg/dL from baseline, (2) a relative increase in SCr levels by ≥50% from baseline, or (3) a urine output reduced to ≤0.5 mL/kg/h for at least 6 hours.[7] Nevertheless, different definitions using varying SCr thresholds exist. Disparities in the definition of CIN have contributed to the debate about the frequency and importance of CIN. Ultimately, all definitions of

From the Department of Radiology and Radiological Science (J.L.W., R.W.K., S.E.L., P.L.Z., C.N.D.C., P.C., U.J.S.), Division of Cardiology, Department of Medicine (S.E.L., P.L.Z., U.J.S.), Medical University of South Carolina, Charleston; and Department of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Frankfurt, Germany (J.L.W., T.J.V.).

Correspondence to U. Joseph Schoepf, MD, Department of Radiology and Radiological Science, Medical University of South Carolina, Ashley River Tower, MSC 226, 25 Courtenay Drive, Charleston, SC 29425. E-mail schoepf@musc.edu

(*Circulation.* 2015;132:1931-1936. DOI: 10.1161/CIRCULATIONAHA.115.014672.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.014672**

contrast-induced AKI are arbitrary and based on laboratory testing. They are useful for statistical comparison in clinical trials but bear little meaning for an individual patient, where only hard outcomes such as dialysis, chronic renal impairment, or kidney-related death are what really matter.

Risk Factors

The widely accepted primary risk factor for CIN is preexisting renal insufficiency with reduced nephron capacity.[4] Several other parameters have been identified as risk factors for AKI but have not been established for CIN. Diabetes mellitus, patient dehydration, and congestive heart failure increase the risk for AKI.[4] Severe transient hypotension and age >80 years have also been considered risk factors for AKI. A dose-dependent risk increasing with CM volume is commonly presumed. Laskey et al have proposed using the ratio of CM volume to creatinine clearance or eGFR as a significant and independent predictor for CIN after percutaneous coronary intervention.[8] Others have suggested that the amount of CM per nephron, approximated by mgI/eGFR, is the best metric for contrast dosage toxicity.[9,10] However, the influence of these risk factors on CIN especially after intravenous CM administration has been challenged by recent studies.[2–4]

Incidence of Acute Kidney Injury Following Intra-Arterial Versus Intravenous Contrast Media Administration

Multiple large-scale studies have demonstrated that the route of administration of CM (intra-arterial versus intravenous) and type of procedure (eg, catheter-based angiography versus CT imaging) have a substantial impact on the incidence of AKI.[11,12] Due to multiple factors, the incidence of AKI is substantially higher following catheter-based procedures with intra-arterial CM administration compared to imaging studies with intravenous CM administration.[10] Several explanations for this observation have been proposed.[13] Patients who undergo catheter-based angiography tend to have more advanced vascular disease than those receiving only intravenous CM and thus have a higher risk of AKI. The invasive nature of catheter angiography, frequently involving manipulation in the aorta, can cause AKI which may be erroneously diagnosed as CIN. Cholesterol crystals, aortic plaque fragments, and thrombi may be physically dislodged, leading to microembolization of the renal parenchyma.[14] In addition, catheter-based procedures may be complicated by transient hypotension or reduced cardiac output leading to postinterventional AKI, which may be misinterpreted as CIN.[15,16] Finally, intra-arterial CM injection is associated with a higher peak iodine concentration in the renal vasculature. While this has been linked to an increased risk of AKI in some studies, the association remains controversial.[11,12] Nevertheless, due to these considerations, the terms postcatheter nephropathy or catheter-induced nephropathy have been proposed to replace contrast-induced nephropathy when referring to deterioration of renal function in patients after catheterization.

The conventional wisdom regarding intravenous CM administration and CIN has further been called into question by recent studies comparing outcomes in large control groups of patients undergoing noncontrast enhanced CT compared to those having contrast-enhanced CT.[4,5] There is increased recognition of daily fluctuations in baseline SCr levels which tend to be more distinct in patients with reduced baseline renal function and may be falsely interpreted as CIN if SCr levels rise in close association with CM administration.[4,5] This aspect alone suggests that the risk of AKI from CM, in particular when administered intravenously for contrast-enhanced CT, has been exaggerated by older, noncontrolled studies that did not account for background fluctuations in renal function. A large meta-analysis of controlled studies included more than 25 000 patients and found equal or lower rates of AKI following contrast-enhanced CT compared to noncontrast enhanced CT.[4] This was true even for subgroup analyses including different definitions of AKI and those with preexisting diabetes or renal insufficiency.[4]

Such meta-analyses of nonrandomized investigations bear the risk of selection bias, since patients considered at risk for AKI may be more likely to undergo noncontrast enhanced CT.[1] Thus, large-scale propensity score–based matching studies were recently performed to counteract such potential bias.[2,3] After evaluating 21 346 patients, McDonald et al did not find an increased risk of AKI, emergent dialysis, or 30-day mortality between patients who underwent contrast-enhanced CT and those who did not, even among patients with compromised renal function or predisposing comorbidities.[2] In a similar propensity score–matched study, McDonald et al similarly observed that the risk of AKI was independent of intravenous CM administration, even in patients with a severely reduced eGFR.[3] Using propensity matching in 12 508 patients, Davenport et al also did not observe an increased risk for AKI in patients with normal renal function after intravenous CM administration for CT, but they reported an increased incidence of AKI in patients with a baseline SCr level ≥1.5 mg/dL or eGFR below 30 mL/min/1.73 m^2 following contrast-enhanced CT compared with patients who underwent noncontrast enhanced CT.[17,18] Several key methodological differences between the approaches by McDonald et al and Davenport et al may partially explain their differing results.[3] While these studies highlight the controversial nature of this ongoing debate, a common major conclusion is that intravenous CM administration during contrast-enhanced CT does not cause AKI in patients with normal renal function.[2,3,17,18]

Is the Use of Contrast Material Associated with Adverse Clinical Outcomes?

The occurrence of postcontrast AKI has been associated with both short- and long-term adverse outcomes.[4,7,13] Nevertheless, the results of most of these studies were based on postinterventional AKI.[7,13] Following cardiac catheterization, in-hospital and 1-year mortality increase 2- to 5-fold in patients experiencing postinterventional AKI compared to those without.[19,20] However, Rudnick and Feldman have cautioned that this does not prove a direct causal relationship between CM use and AKI, due to the confounding interaction of risk factors and other comorbidities in patients undergoing catheter angiography.[21] In comparison, the hard outcomes of emergent dialysis and 30-day mortality were shown to be no different between individuals having closely matched demographic and clinical characteristics either with or without intravenous CM exposure.[2] Thus, AKI is associated with a worsened clinical outcome, but current research suggests that this is independent of intravenous CM administration.[2,3]

Table 1. Recommendations for Prevention of CIN

1. Identify risk factors for CIN
   - a. eGFR <30 mL/min per 1.73 m^2
     - i. Suboptimal hydration status
     - ii. Planned intra-arterial administration
       1. Often higher contrast volume
       2. Greater burden of underlying cardiovascular disease
       3. Greater likelihood of hemodynamic compromise
       4. Likelihood of atheromatous emboli
     - iii. Known or suspected acute renal failure
2. For intra-arterial contrast administration in patients with eGFR <30 mL/min per 1.73 m^2 consider to
   - a. Manage medications
     - i. Withhold potentially nephrotoxic drugs such as aminoglycoside antibiotics, antirejection medications, and nonsteroidal anti-inflammatory agents (NSAID)
   - b. Manage intravascular volume (avoid dehydration)
     - i. Administer a total of at least 1 L of isotonic (normal) saline beginning at least 3 h before and continuing at least 6–8 h after the procedure, if cardiovascular status allows
   - c. Select an alternative imaging examination providing similar information, if available
3. While administrating iodinated radiographic contrast media
   - a. Minimize volume, assess dose using volume (mL)/eGFR[8]
   - b. Use low- or iso-osmolar contrast agents
4. Postprocedure: follow-up
   - a. Obtain SCr 48 h postprocedure
   - b. Consider holding appropriate medications until renal function returns to normal; ie, metformin, NSAID
5. If CIN occurs, intensify therapy for cardiovascular disease risk factors

CIN indicates contrast-induced nephropathy; eGFR, estimated glomerular function; and SCr, serum creatinine concentration. The above table is based on authors' experience, literature review, and consensus of the Society for Cardiovascular Angiography and Intervention (SCAI) in 2006.[22,23]

Preventive Measures

While the causality between CM application and AKI remains controversial, clinicians must provide optimal individual care in patients who have both potential risks and benefits from contrast-enhanced imaging studies or interventions (Table 1). The official guidelines published by the American College of Radiology and the European Society of Urogenital Radiology both recommend prophylactic intravenous hydration (1.0–1.5 mL/kg/h) in patients at risk for AKI at least 6 hours before and after CM administration.[6,22] Since CM are osmotic diuretics, they can potentiate the prerenal effects of dehydration, a risk factor for AKI which can be mitigated by optimal patient hydration. It has also been reported that intravenous hydration represents an effective preventive measure in patients at risk for CIN.[23] Consequently, there has been widespread implementation of aggressive hydration protocols in the context of CM administration. However, the recent controversial discussion regarding the correlation of CM administration and AKI/CIN also challenges the efficacy of such preventive measures.[4] Some of the studies reporting a positive effect suffered from substantial bias. Concrete evidence for the appropriateness of hydration in patients undergoing contrast-enhanced imaging is still missing. There is a lack of randomized trials with adequate statistical power to prove the value of hydration for preventing CIN. Moreover, there is currently no consensus on the value of other prophylactic measures such as antioxidant therapy (ie, n-acetylcysteine and sodium bicarbonate) or vasodilators (to reverse medullary ischemia). Most data suggest that these measures are not effective.[6,22,24,25] Thus, no preventive measures can be strongly recommended for current clinical practice, particularly in patients who could be harmed by rapid administration of intravenous fluids, eg, those with congestive heart failure.

Imaging with Reduced Contrast

Independent of the discussion regarding the incidence and clinical relevance of CIN, recent technological innovation has enabled new imaging techniques that provide comparable image quality while allowing for drastic reductions in CM requirements. Lowering the x-ray tube voltage is chiefly used to reduce radiation exposure during CT but coincidentally also provides opportunities for significant CM volume reduction. Scanning at lower energy

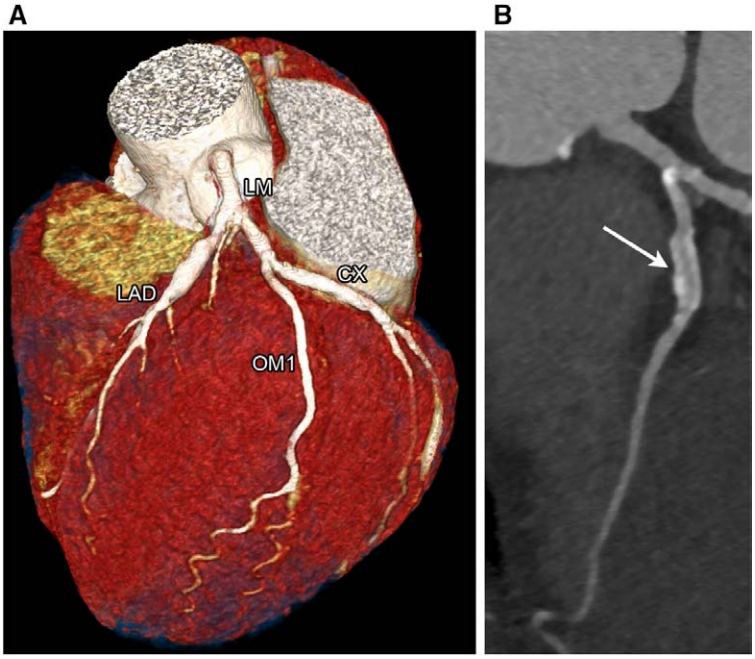

Figure 1. Coronary computed tomography (CT) angiography study in an 84-year-old woman (**A**, volume rendered image of left coronary tree) with multiple coronary calcifications (**B**, curved multiplanar reformat of proximal left anterior descending artery) showing mural calcification (arrow) but without significant stenosis. Study was performed with third-generation dual-source CT in high-pitch mode at 70 kV using iterative reconstruction, which enabled reducing the effective radiation dose to 0.31 mSv and the contrast media volume to 40 mL.

levels results in increased intravascular iodine attenuation,[26] translating into greater vascular contrast with lower iodine concentrations. New iterative image reconstruction algorithms mitigate the increased image noise that normally results from acquisition at low tube voltage settings.[26] In combination, the latest generation of CT imaging platforms provides similar image quality with low radiation and low contrast exposure, compared to imaging with standard tube voltage and CM volumes (Figures 1 and 2).[26] In addition, high-pitch acquisition and dual-energy CT imaging with various postprocessing techniques improve imaging quality.[26]

Conclusion

The risk of AKI from CM, especially when administered intravenously for the purpose of noninvasive imaging, has been exaggerated by previous,

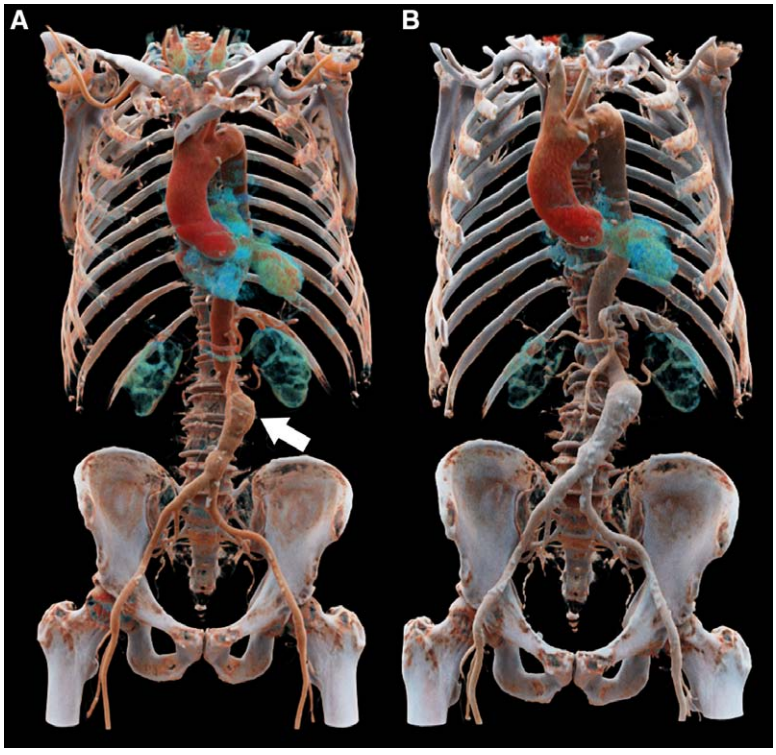

Figure 2. Comparison of computed tomography (CT) studies of the thoracoabdominal aorta in a 90-year-old man (reconstructed with Cinematic Rendering, Siemens - not intended for clinical use). The patient underwent follow-up imaging due to a known fusiform infrarenal abdominal aortic aneurysm (arrow). The first scan (**A**) was performed with second-generation dual-source CT with a tube voltage of 120 kV and 100 mL contrast volume. The follow-up scan five years later (**B**) was conducted with third-generation dual-source CT with a reduced tube voltage of 80 kVp and contrast material volume of 40 mL. The effective radiation dose was reduced from 13.39 mSv in the first scan to 3.32 mSv in the follow-up scan. Image quality was diagnostic in both studies.

noncontrolled studies. More recent evidence from controlled studies suggests that the risk is likely nonexistent in patients with normal renal function. There may be a risk in patients with renal insufficiency; however, even in this patient population, the risk of contrast-induced AKI is probably much lower than is widely accepted. Even though there are conflicting data, it is still prudent to exert caution in patients with significant renal impairment (a baseline creatinine of >2.0mg/dL or an eGFR of <30mL/min/1.73m^2). Hydration is the protective regimen with the strongest, albeit not uncontested, supporting evidence. The benefits of diagnostic information gained from contrast-enhanced imaging need to be balanced by the potential risk of contrast-induced AKI for the individual patient.

Acknowledgments

The authors sincerely thank Dr Xiaoyan Chen, Andreas Wimmer, and Torsten Lowitz from Siemens Healthcare for their assistance in figure preparation.

Disclosures

U. Joseph Schoepf, MD is a consultant for or receives research support from Astellas, Bayer, Bracco, GE, Medrad, and Siemens. The other authors have no conflicts of interest to disclose.

References

1. Newhouse JH, RoyChoudhury A. Quantitating contrast medium-induced nephropathy: controlling the controls. *Radiology*. 2013;267:4–8. doi: 10.1148/radiol.13122876.
2. McDonald RJ, McDonald JS, Carter RE, Hartman RP, Katzberg RW, Kallmes DF, Williamson EE. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology*. 2014;273:714–725. doi: 10.1148/radiol.14132418.
3. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. *Radiology*. 2014;271:65–73. doi: 10.1148/radiol.13130775.
4. McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, Kallmes DF. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology*. 2013;267:119–128. doi: 10.1148/radiol.12121460.
5. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, Williamson EE, Kallmes DF. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology*. 2013;267:106–118. doi: 10.1148/radiol.12121823.
6. Radiology ACo. ACR Manual on Contrast Media. 2013; version 9: 81–98. 2013.
7. Lakhal K, Ehrmann S, Chaari A, Laissy JP, Régnier B, Wolff M, Pajot O. Acute Kidney Injury Network definition of contrast-induced nephropathy in the critically ill: incidence and outcome. *J Crit Care*. 2011;26:593–599. doi: 10.1016/j.jcrc.2011.05.010.
8. Laskey WK, Jenkins C, Selzer F, Marroquin OC, Wilensky RL, Glaser R, Cohen HA, Holmes DR Jr; NHLBI Dynamic Registry Investigators. Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50:584–590. doi: 10.1016/j.jacc.2007.03.058.
9. Sherwin PF, Cambron R, Johnson JA, Pierro JA. Contrast dose-to-creatinine clearance ratio as a potential indicator of risk for radiocontrast-induced nephropathy: correlation of D/CrCL with area under the contrast concentration-time curve using iodixanol. *Invest Radiol*. 2005;40:598–603.
10. Solomon R. Contrast-induced acute kidney injury: is there a risk after intravenous contrast? *Clin J Am Soc Nephrol*. 2008;3:1242–1243. doi: 10.2215/CJN.03470708.
11. Dong M, Jiao Z, Liu T, Guo F, Li G. Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. *J Nephrol*. 2012;25:290–301. doi: 10.5301/jn.5000067.
12. Karlsberg RP, Dohad SY, Sheng R; Iodixanol Peripheral Computed Tomographic Angiography Study Investigator Panel. Contrast medium-induced acute kidney injury: comparison of intravenous and intra-arterial administration of iodinated contrast medium. *J Vasc Interv Radiol*. 2011;22:1159–1165. doi: 10.1016/j.jvir.2011.03.020.
13. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, Pannu N, Manns BJ, Klarenbach SW, Hemmelgarn BR; Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation*. 2011;123:409–416. doi: 10.1161/CIRCULATIONAHA.110.970160.
14. Keeley EC, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol*. 1998;32:1861–1865.
15. Bruce RJ, Djamali A, Shinki K, Michel SJ, Fine JP, Pozniak MA. Background fluctuation of kidney function versus contrast-induced nephrotoxicity. *AJR Am J Roentgenol*. 2009;192:711–718. doi: 10.2214/AJR.08.1413.
16. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *AJR Am J Roentgenol*. 2008;191:376–382. doi: 10.2214/AJR.07.3280.
17. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. *Radiology*. 2013;268:719–728. doi: 10.1148/radiol.13122276.
18. Davenport MS, Khalatbari S, Cohan RH, Ellis JH. Contrast medium-induced nephrotoxicity risk assessment in adult inpatients: a comparison of serum creatinine level- and estimated glomerular filtration rate-based screening methods. *Radiology*. 2013;269:92–100. doi: 10.1148/radiol.13122462.
19. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542–1548.
20. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
21. Rudnick M, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences? *Clin J Am Soc Nephrol*. 2008;3:263–272. doi: 10.2215/CJN.03690907.
22. Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, Almén T, Aspelin P, Bellin MF, Clement O, Heinz-Peer G; Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol*. 2011;21:2527–2541. doi: 10.1007/s00330-011-2225-0.
23. Balemans CE, Reichert LJ, van Schelven BI, van den Brand JA, Wetzels JF. Epidemiology of contrast material-induced nephropathy in the era of hydration. *Radiology*. 2012;263:706–713. doi: 10.1148/radiol.12111667.
24. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA*. 2008;300:1038–1046. doi: 10.1001/jama.300.9.1038.
25. Gurm HS, Smith DE, Berwanger O, Share D, Schreiber T, Moscucci M, Nallamothu BK; BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium). Contemporary use and effectiveness of N-acetylcysteine in preventing contrast-induced nephropathy among patients undergoing percutaneous coronary intervention. *JACC Cardiovasc*

Interv. 2012;5:98–104. doi: 10.1016/j.jcin.2011.09.019.
26. Meyer M, Haubenreisser H, Schoepf UJ, Vliegenthart R, Leidecker C, Allmendinger T, Lehmann R, Sudarski S, Borggrefe M, Schoenberg SO, Henzler T. Closing in on the K edge: coronary CT angiography at 100, 80, and 70 kV-initial comparison of a second- versus a third-generation dual-source CT system. *Radiology*. 2014;273:373–382. doi: 10.1148/radiol.14140244.
27. Schweiger MJ, Chambers CE, Davidson CJ, Zhang S, Blankenship J, Bhalla NP, Block PC, Dervan JP, Gasperetti C, Gerber L, Kleiman NS, Krone RJ, Phillips WJ, Siegel RM, Uretsky BF, Laskey WK. Prevention of contrast induced nephropathy: recommendations for the high risk patient undergoing cardiovascular procedures. *Catheter Cardiovasc Interv*. 2007;69:135–140. doi: 10.1002/ccd.20964.
28. Solomon R. Contrast-induced acute kidney injury (CIAKI). *Radiol Clin North Am*. 2009;47:783–8, v. doi: 10.1016/j.rcl.2009.06.001.

Contrast-Induced Nephropathy

Julian L. Wichmann, Richard W. Katzberg, Sheldon E. Litwin, Peter L. Zwerner, Carlo N. De Cecco, Thomas J. Vogl, Philip Costello and U. Joseph Schoepf

Circulation. 2015;132:1931-1936
doi: 10.1161/CIRCULATIONAHA.115.014672
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539