Published in final edited form as:

Curr Opin Nephrol Hypertens. 2018 March ; 27(2): 121–129. doi:10.1097/MNH.0000000000000389.

Maximum Allowable Contrast Dose and Prevention of Acute Kidney Injury Following Cardiovascular Procedures

Joe Aoun, MD^{1,2}, Diala Nicolas, PharmD³, Jeremiah R. Brown, PhD⁴, and Bertrand L. Jaber, MD, MS^{1,2}

¹Department of Medicine, St. Elizabeth's Medical Center, Boston, MA

²Department of Medicine, Tufts University School of Medicine, Boston, MA

³Department of Pharmacy, St. Elizabeth's Medical Center, Boston, MA

⁴The Dartmouth Institute for Health Policy and Clinical Practice, Department of Epidemiology, Department of Biomedical Data Science, Geisel School of Medicine at Dartmouth, Lebanon, NH

Abstract

Purpose of review: Contrast-induced acute kidney injury (CI-AKI) is a serious complication. Although non-modifiable and modifiable risk factors have been thoroughly characterized, the utility of the Maximal Allowable Contrast Dose (MACD) has not received adequate attention. The focus of this review is to provide a critical appraisal of this modifiable risk factor.

Recent findings: Several retrospective and prospective cohort studies have demonstrated that the incidence of CI-AKI among patients receiving contrast media in volumes exceeding the MACD is consistently higher compared to those who do not exceed the MACD (an average of 24% vs. 6%). Furthermore, the MACD is independent predictor of CI-AKI and other adverse events. A two-step algorithm incorporating the determination of the MACD and the contrast volume to eGFR ratio prior to a planned cardiovascular procedure is a sound approach to minimize contrast volume and prevent CI-AKI.

Summary: Prevention of CI-AKI must remain a clinical priority. Intra-procedural preventative measures should include a priori calculation of the MACD and contrast volume to eGFR ratio to limit contrast volume. Other measures may include the adoption of the trans-radial approach, the use of automated contrast injectors and small catheters to limit contrast volume, the use of low-osmolar contrast agents, and if necessary the use of staged procedures. We call for the system-wide implementation of evidence-based care bundles to prevent CI-AKI.

Keywords

contrast media; acute kidney injury; prevention

Introduction

Contrast-induced acute kidney injury (CI-AKI) is a serious complication following the intravenous or intra-arterial administration of iodinated contrast media. The incidence of CI-AKI is estimated at 3 to 19% in patients undergoing cardiovascular procedures (1), and it confers an independent risk for adverse clinical outcomes, including increased healthcare expenditures, prolonged hospital length of stay (2), and in-hospital mortality (3). Once diagnosed, the clinical management of CI-AKI is largely supportive.

Non-modifiable risk factors for CI-AKI include advanced age, diabetes mellitus, and pre-existing kidney disease. Two common modifiable risk factors include extra-cellular fluid volume depletion, and contrast agents used (type and volume) (4). Extracellular fluid volume expansion is the cornerstone for prevention of CI-AKI (4,5). Intravenous fluid administration increases intravascular volume, enhances renal blood flow and promotes diuresis. This ultimately decreases the contact duration of contrast media with the nephron, reduces activation of the renin angiotensin aldosterone system, and diminishes the inhibition of vasodilators. Although normal saline has long been considered the standard of care, sodium bicarbonate has been hypothesized to provide an additional benefit because it produces an alkaline environment, where formation of reactive oxygen species is diminished (5,6). Whether sodium bicarbonate is superior to normal saline remains a matter of ongoing debate (7). As for pharmacological prophylaxis, some drugs have been proposed to mitigate the risk of CI-AKI by opposing vasoconstriction, enhancing renal blood flow or reducing formation of reactive oxygen species (8). While no medication has been proven to have significant and consistent benefit, N-acetyl cysteine is widely used for the prevention of CI-AKI, and might exert antioxidant and vasodilatory effects (7). Statins, through their pleiotropic anti-inflammatory properties, have recently been shown to be of potential benefit in this setting (5,7). However, more evidence is needed before statins can be endorsed for the prevention of CI-AKI (9-11).

While multiple patient-related factors increase the risk of CI-AKI, clinicians should address any modifiable risk factors, including contrast type and volume (12). The focus of this review is to provide a critical appraisal of one of the modifiable risk factors, contrast volume, focusing on the Maximum Allowable Contrast Dose (MACD), a concept first introduced in 1989 (13).

Contrast Media Considerations

Contrast agents are classified as ionic and non-ionic (4,6,14,15). Ionic agents dissociate into negatively charged ions and positively charged ions. Therefore, ionic agents contain more particles per milliliter, leading to a higher osmolality compared to non-ionic agents. Non-ionic agents do not dissociate but have polar hydroxyl groups that impart water solubility. All contrast agents have the basic structure of a triiodinated benzene ring (Figure 1A), where an iodine atom is attached to carbon atoms 2, 4 and 6. Carbon atoms 1, 3 and 5 are attached to different side chains, which determine the compound's solubility, osmolality, protein binding and side effect profile.

Ionic monomers were the first contrast agents to be developed and marketed. These are high-osmolar agents, with an osmolality that is 5 to 8 times that of serum. Soon after these agents were introduced into clinical practice, it became apparent that their high osmolality could potentially cause serious adverse effects. It was hypothesized that the toxicity of contrast agents would decrease if their osmolality were reduced to approach that of serum; hence low-osmolar contrast agents were developed. Reducing the osmolality of contrast media can be achieved either by producing non-ionic compounds or by joining 2 monomers to create a dimer (Figure 1B). The first low-osmolar agents to be produced were ionic dimers followed by non-ionic monomers. In order to further reduce osmolality, non-ionic dimers were most recently developed. Although these newer agents are iso-osmolar and least likely to cause adverse effects, a randomized control trial comparing a low-osmolar to an iso-osmolar contrast agent was not able to demonstrate a significant difference in the incidence of CI-AKI in high risk patients (eGFR 20-59 mL/min/1.73 m²) (16).

Regarding the pathophysiology of nephrotoxicity, contrast media generally stimulate the release of endothelin and other vasoconstrictors while simultaneously blocking the release of vasodilators such as prostaglandins and nitric oxide (4). High-osmolar contrast agents are associated with a higher risk of CI-AKI compared to low-osmolar and iso-osmolar agents (12), and are not used for cardiovascular procedures. This is due to the fact that high-osmolar agents dissociate into particles that induce osmotic diuresis, leading to ischemic injury and formation of reactive oxygen species. The evolution of contrast media through the reduction of osmolality has had an impact on lowering the incidence of adverse effects, including CI-AKI (12).

Critical Appraisal of Studies Evaluating the Utility of MACD

The volume of contrast administered during a cardiovascular procedure is crucial. No single, universally accepted threshold is known to cause CI-AKI. Over the years, the suggested volume cut-off has varied from a fixed volume of 125 mL (17) to a relative, weight-based volume of 3 mL/kg (18). Low-osmolar contrast agents are widely used in clinical practice, with an observed mean administered volume ranging from 30 to 140 mL (19). Of note, the use of low-osmolar contrast agents at a volume of greater than 30 mL has been associated with an increased incidence of CI-AKI (20).

The Maximal Allowable Contrast Dose (MACD) was first conceptualized by Cigarroa et al in 1989 (13), and defined by the following empiric formula: $\text{MACD} = 5 \text{ mL} \times \text{body weight (in kg)} / \text{serum creatinine (in mg/dL)}$, with a maximum dose of 300 mL. The authors hypothesized a relationship between the contrast dose, the body weight and the baseline kidney function, but there was no scientific basis for selecting the coefficient of 5. In this seminal but rather small single-center study, 110 patients with chronic kidney disease (baseline serum creatinine $\geq 1.8 \text{ mg/dL}$) deemed at increased risk for CI-AKI were included. The definition of AKI preceded standardized published definitions, and was based on an absolute increase in the serum creatinine by 1 mg/dL during the first five days. The authors observed a 10-fold increase in the incidence of CI-AKI among patients receiving contrast media in volumes exceeding the MACD compared to those who did not exceed the MACD (21% vs. 2%). Of note, 30 (26%) patients were excluded from the analysis as the serum

creatinine was only measured for the first two days following the procedure. Among a subset of patients with diabetes, the incidence of CI-AKI was even higher when the contrast volume exceeded the MACD (38% vs. 6%). The authors concluded that among patients with diabetes and kidney disease, it may be preferable to perform angiography as a staged procedure or utilize alternative non-contrast imaging techniques to obtain the desired information rather than to exceed the MACD.

This concept was validated 13 years later by Freeman et al, where both a development and a test set were derived from a multicenter registry of 16,592 percutaneous interventions to examine the association between the MACD and dialysis-requiring CI-AKI (21). Among the 41 (0.44%) patients who developed dialysis-requiring CI-AKI, there was a higher prevalence of diabetes mellitus, chronic kidney disease, and heart failure. 63% of patients who required dialysis received contrast volume that exceeded the MACD, compared to only 11% among those who did not require dialysis. After adjustment for confounding factors, the MACD was the strongest independent predictor of dialysis-requiring CI-AKI with an adjusted odds ratio of 6.2 (and a 95% confidence interval of 3.0 to 12.8). Of note, this study did not mention the use of prophylactic measures to prevent CI-AKI, such as normal saline and N-acetyl cysteine.

In a single-center prospective cohort study by Marenzi et al, 561 patients with acute ST elevation myocardial infarction underwent percutaneous interventions and the contrast dose was left to the discretion of the interventional cardiologists (22). While there was no significant difference in the prevalence of diabetes mellitus and hypertension between patients receiving contrast volume that exceeded the MACD compared to those who did not, those who exceeded the MACD had a lower mean eGFR (62 vs. 80 mL/min/1.73 m²) (22). CI-AKI was defined as a relative increase in the serum creatinine by 25% during the first three days following the procedure. Patients whose contrast dose exceeded the MACD had a higher incidence of CI-AKI (45% vs. 13%), and were at an increased risk for in-hospital mortality (21.4% vs. 0.9%) (22).

In a single center prospective cohort study of 9,910 patients undergoing percutaneous coronary intervention, Brown et al divided patients according to whether the contrast volume to MACD ratio was less or greater than 1.0 and examined the incidence of CI-AKI and other post-procedural adverse events (23). CI-AKI was defined as an increase in serum creatinine by 0.3 mg/dL or 50%, or dialysis requirement. The majority of patients had a baseline eGFR of > 60 mL/min/1.73 m². Patients in whom the contrast volume did not exceed the MACD had a lower prevalence of hypertension, heart failure and coronary artery disease and more preserved eGFR. The administration of contrast volume that exceeded the MACD was an independent risk factor for CI-AKI, and there was a linear increase in the unadjusted risk with higher contrast volume (13%, 20% and 27% for a contrast volume to MACD ratio of 1.0-1.5, 1.5-2.0, and > 2.0, respectively). Furthermore, the adjusted odds ratio for CI-AKI was 1.60, 2.02, and 2.94 following exposure to a contrast volume to MACD ratio of 1.0-1.5, 1.6-2.0, and > 2.0, respectively. Patients who received a contrast volume to MACD ratio of greater than 1.0 had higher rates of AKI requiring dialysis (1.5% vs. 0.2%), cardiac events (13.4% vs. 10.2%), bleeding complications (8.4% vs. 4.1%), and in-hospital death (3.4% vs. 1.7%) (23).

In a retrospective cohort study, Ogata et al analyzed 100 patients with advanced stage-4 chronic kidney disease (baseline eGFR < 30 mL/min/1.73 m²) who had undergone elective percutaneous coronary intervention (24). The authors stratified patients according to the contrast volume to eGFR ratio and the MACD, and divided them into three mutually exclusive groups: a low-dose group (contrast volume to eGFR ratio < 1.0), a medium-dose group (contrast volume to eGFR ratio > 1.0 but < MACD), and a high-dose group (contrast volume > MACD) (24). Baseline characteristics were well balanced between the three groups. The incidence rate of CI-AKI, as defined by an increase in serum creatinine by 0.5 mg/dL or 25% 48 hours following the procedure, occurred in 11% of patients, was 0%, 11%, and 23% in the low-dose, medium-dose, and high-dose group, respectively. Furthermore, the rate of the composite outcome of dialysis requirement, myocardial infarction or death increased from 0% to 14%, and 31% in the three respective groups (24). The authors concluded that among patients with advanced CKD, aiming for a contrast volume to eGFR ratio of less than 1.0 might reduce the incidence of CI-AKI and achieve better clinical outcomes following elective percutaneous coronary intervention.

Raposeiras-Roubín et al performed a retrospective cohort study of 940 patients with acute coronary syndrome undergoing coronary angiography, in an effort to establish a safe contrast dose based on the absolute and relative contrast volume using the MACD and the contrast volume to eGFR ratio, and develop a simple strategy for contrast dosing (25). CI-AKI, defined by an increase in the serum creatinine by 0.5 mg/dL within 72 hours, developed in 54 (5.7%) patients. The incidence of CI-AKI was higher when the contrast volume exceeded the MACD (36.1% vs. 3.6%). Moreover, every 10-mL increase in contrast volume was associated with a 5%-increase in the risk of CI-AKI. The cut-off level for the absolute contrast volume with greatest discriminative power was 158 mL, with a sensitivity and specificity of 74% and 52%, respectively. The authors also found that using a contrast volume exceeding 50% of the MACD as a predictor cut-off point had a sensitivity and specificity of 74.1% and 65.6%, respectively. Furthermore, every 0.1 unit increase in the contrast volume to eGFR ratio was associated a 4.9%-increased risk of CI-AKI, and the cut-off level with greatest discriminative power was 2.7, with a sensitivity and specificity of 74.1% and 64.6%, respectively. The authors proposed a two-step algorithm to stratify the risk of CI-AKI according to the MACD and the contrast volume to eGFR ratio (Figure 3). The authors found that their proposed algorithm had a higher positive predictive value than the Mehran risk score (40.7% vs. 8.8%) with similar sensitivity (90.7% vs. 83.3%). This proposed two-step algorithm requires further study and external validation.

Laskey et al examined an unselected cohort of 3,179 consecutive patients undergoing percutaneous coronary intervention, and found that a contrast volume to creatinine clearance ratio of greater than 3.7 was a fair discriminator for predicting CI-AKI, as defined by an increase in serum creatinine by > 0.5 mg/dL within 48 hours, and was independently associated with development of CI-AKI with an odds ratio of 3.84 (26).

In a multi-center cohort study of 58,957 patients undergoing cardiovascular procedures, Gurm et al found that the contrast volume to creatinine clearance ratio performed significantly better than the MACD at predicting CI-AKI (27). Moreover, a contrast volume to creatinine clearance ratio cut-off of > 3 was associated with an adjusted odds ratio of 1.46

for CI-AKI, and of 1.89 for dialysis requirement. The authors concluded that this ratio should be less than 2 and not exceed 3 for any angiographic procedure.

Figure 2 displays the incidence rate of CI-AKI observed in the above mentioned observational studies among patients who received contrast volume that did or did not exceed the MACD. The observed variable rates suggest significant heterogeneity amongst the studies, including variable study design, sample size, AKI definition, preexisting comorbidities, and implemented preventative measures. In these observational studies, the 'contrast volume' variable suffers from confounding by indication as patients undergoing emergent rather than elective percutaneous coronary interventions were more likely to be hemodynamically unstable and require greater contrast volume (i.e., for coronary angioplasty and insertion of stents). Nevertheless, all these observational studies point to the fact that modulating the contrast volume is a potentially modifiable risk factor for CI-AKI, and a measure of excessive contrast volume (e.g., MACD or contrast volume to eGFR ratio) needs to be determined a priori by the operator, and ideally not exceeded during a cardiovascular procedure.

Other Important Considerations Related to Contrast Media

The route of administration is another important consideration as contrast media is more nephrotoxic when administered intra-arterially (28,29). This effect is hypothesized to be due in part to a higher intra-renal concentration of contrast media achieved acutely after intra-arterial rather than intravenous injection, and to potential renal atheroembolic disease, which can occur in the setting of intra-arterial instrumentation. This question has not been properly examined and requires further study.

Furthermore, the use of a trans-femoral (Seldinger technique) or trans-radial (Sones technique) approach to cardiac catheterization might affect the risk of post-procedure AKI. Peri-procedural bleeding, especially retroperitoneal bleeding in the setting of a trans-femoral approach, is an emerging risk factor for the development of post-procedural AKI, and the trans-radial access has been associated with a lower incidence of vascular access-related bleeding complications and all-cause mortality in a large randomized controlled trial of 8404 patients with acute coronary syndrome (30), and a lower risk of post-procedural AKI in a large meta-analysis of more than 12,000 patients with an average incidence rate of 10.3% vs. 4.6% (31). These studies call for the more widespread use of the trans-radial approach to cardiac catheterization, when technically feasible, which might also minimize the risk of renal atheroembolic disease as wires would not traverse the abdominal aorta.

Call for Refinement of CI-AKI Prediction Models

The reliability of both the absolute and relative contrast volume as a modifiable risk factor and independent predictor of AKI call for the refinement of existing prediction models for CI-AKI. The Mehran risk score, published more than a decade ago, was developed to predict AKI following percutaneous coronary intervention, and has been widely adopted (32). For this risk prediction tool, points are given for hypotension, use of intra-aortic balloon pump, congestive heart failure, age > 75, anemia, volume of contrast, and serum creatinine (> 1.5

mg/dL). A recently developed risk prediction tool incorporates additional risk factors such as acute coronary syndrome, urgent catheterization, history of prior AKI, use of loop diuretics, and hypoalbuminemia (33). Novel risk scores should consider the incorporation of the MACD, proteinuria, an important marker of kidney damage that is a known risk factor for AKI independent of eGFR (34), and use of blockers of the renin angiotensin aldosterone system (RAAS), which have also been associated with an increased risk of CI-AKI (35).

Current Clinical Practice Guidelines for Prevention of CI-AKI

For the prevention of CI-AKI, the *2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention* state that patients should be assessed for risk of CI-AKI prior to the procedure; patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration; and in patients with CKD (creatinine clearance < 60 mL/min), the volume of contrast media should be minimized (36). Similarly, the *2012 KDIGO Clinical Practice Guidelines* on AKI focus on other measures to prevent CI-AKI following angiographies. These measures include the use of biplane, avoidance of test injections, unnecessary projections, and ventriculography, use of isotonic contrast-media for renal artery injections, use of CO₂ in venous and below diaphragm for arterial procedures, use of selective catheterizations when appropriate, and reducing aortic flow and contrast medium volume by temporal occlusion of femoral arteries with tourniquets when performing aortography (37). Future guidelines for prevention of CI-AKI following percutaneous coronary intervention should consider incorporating a more objective measure of contrast media volume such as the MACD or the contrast volume to creatinine clearance ratio, and promote the staging of procedures when appropriate, and promote the trans-radial arterial catheterization method as the default approach.

The National Quality Forum has defined CI-AKI as a patient safety measure, and has issued a safe practice guideline aimed at reducing the contrast medium-related adverse events (38). Furthermore, the Center of Medicare & Medicaid Services recently proposed the addition of CI-AKI as a new condition to the list of hospital acquired conditions; this condition will be subject to reduced payment provisions under the Inpatient Prospective Payment System, nevertheless, this measure has not yet been released (39). We also propose that CI-AKI should become a hospital-based quality of care indicator with pay-per-performance ramifications, and call for system-wide implementation of evidence-based care bundles to prevent CI-AKI. The approach should be similar to what has been implemented across acute care hospitals in the US to reduce morbidity and mortality, such as the central line, ventilator and sepsis management bundles promoted by the Institute for Healthcare Improvement (40). In high-risk populations, CI-AKI prevention bundles should incorporate hydration with normal saline or sodium bicarbonate prior to contrast administration, the temporary discontinuation of RAAS blockers, the use of low- or iso-osmolar contrast agents, and the minimization of contrast volume. Figure 3 provides a two-step algorithm that incorporates the MACD and the contrast volume to eGFR ratio, as an approach to minimize contrast volume.

Incorporating the MACD into Practice-Based Care Bundles to Prevent CI-AKI: Lessons Learned from Quality Improvement Reports

The Blue Cross Blue Shield of Michigan Cardiovascular Consortium reported on a demonstration project aimed at reducing the incidence of CI-AKI following percutaneous coronary intervention (41). In this quality improvement report that included 5 hospitals, patients were deemed at high risk for CI-AKI if they had diabetes, a serum creatinine ≥ 2 mg/dL, peripheral vascular disease, heart failure, or cardiogenic shock. The consortium proposed management guidelines including the use of aggressive intravenous hydration and consideration for N-acetyl cysteine; determining the MACD and not exceeding it by performing biplanar coronary angiography and avoiding unnecessary images; considering staged procedures (several days after the first procedure); the use of small catheters to limit contrast volume; and the use of low-osmolar contrast agents. There was a baseline assessment period and an intervention period, and workgroup meetings focused on selection of quality indicators, use of bedside tools for quality improvement and risk assessment (i.e., use of the MACD), site visits, and feedback on outcomes. Over a 4-year period, the percentage of cases exceeding the MACD steadily declined, and this was paralleled by a progressive decline in the incidence of CI-AKI. The study demonstrates that the implementation of a regional continuous quality improvement program is feasible and by enhancing adherence to quality of care indicators, outcomes of percutaneous coronary intervention can be improved. This calls for the implementation of such evidence-based care bundles to prevent CI-AKI.

The Northern New England Cardiovascular Disease Study Group led a regional quality improvement effort to achieve a cost-effective and sustainable decrease in the incidence of CI-AKI (42). This quality improvement project was conducted over 6 years and comprised 6 hospitals. Multidisciplinary teams with key stake holders developed interventions with a focus on oral hydration before and after the procedure, pre-procedural standardization of intravenous fluid administration, reducing the fasting period from 12 hours to 2-4 hours, minimizing contrast volume administration by calculating the MACD prior to every procedure, and respecting it by limiting contrast media administration during the procedure. The authors reported a 21% (95% confidence interval of 7% to 33%) decrease in the rate of CI-AKI after the intervention. Some of the key barriers to implementation included resistance to amend physician orders that were based on older protocols (42).

Concluding Remarks

In conclusion, prevention of CI-AKI must remain a clinical priority due to the short-term associated morbidity and mortality, and the long-term risk of decline in kidney function (43). In addition to identifying high-risk patients based on their comorbidities and pre-procedural hydration and possible use of N-acetyl cysteine, additional intra-procedural preventative measures (Table 3) should include a priori calculation of the MACD and contrast volume to creatinine clearance or eGFR ratio to limit contrast volume, the adoption of the trans-radial approach, the use of small catheters to limit contrast volume, the use of low- and iso-osmolar contrast agents, and when indicated, the use of staged procedures.

References

1. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. *JACC Cardiovasc Interv.* 2014 1;7(1):1–9. [PubMed: 24456715]
2. Silver SA, Long J, Zheng Y, Chertow GM. Cost of Acute Kidney Injury in Hospitalized Patients. *J Hosp Med.* 2017 2;12(2):70–6. [PubMed: 28182800]
3. Weisbord SD, Palevsky PM. Contrast-Induced Acute Kidney Injury: Short and Long-term Implications. *Semin Nephrol.* 2011 5;31(3):300–9. [PubMed: 21784279]
4. Wong PCY, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. *Int J Cardiol.* 2012 7 12;158(2):186–92. [PubMed: 21784541]
5. Stacul F, van der Molen AJ, Reimer P, Webb JAW, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol.* 2011 12;21(12):2527–41. [PubMed: 21866433]
6. Geenen RWF, Kingma HJ, van der Molen AJ. Contrast-induced nephropathy: pharmacology, pathophysiology and prevention. *Insights Imaging.* 2013 12;4(6):811–20. [PubMed: 24092564]
7. Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, et al. Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2016 3 15;164(6):406–16. [PubMed: 26830221]
8. Faubel S, Chawla LS, Chertow GM, Goldstein SL, Jaber BL, Liu KD, et al. Ongoing clinical trials in AKI. *Clin J Am Soc Nephrol CJASN.* 2012 5;7(5):861–73. [PubMed: 22442183]
9. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol.* 2014 1 7;63(1):71–9. [PubMed: 24076283]
10. Alpert MA. Do statins reduce the risk of contrast-induced acute kidney injury in patients undergoing coronary angiography or percutaneous coronary interventions? *J Am Coll Cardiol.* 2014 1 7;63(1):80–2. [PubMed: 24076280]
11. Han Y, Zhu G, Han L, Hou F, Huang W, Liu H, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol.* 2014 1 7;63(1):62–70. [PubMed: 24076297]
12. Eng J, Wilson RF, Subramaniam RM, Zhang A, Suarez-Cuervo C, Turban S, et al. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2016 3 15;164(6):417–24. [PubMed: 26830055]
13. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med.* 1989 6;86(6 Pt 1):649–52. [PubMed: 2729314]
14. Mukherjee D, Bates E, Roffi M, Moliterno D. Cardiovascular Catheterization and Intervention: A Textbook of Coronary, Peripheral, and Structural Heart Disease. CRC Press; 2010 742 p.
15. Buschur M, Aspelin P. Contrast Media: History and Chemical Properties. *Interv Cardiol Clin.* 2014 7;3(3):333–9. [PubMed: 28582217]
16. Solomon RJ, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, et al. Cardiac Angiography in Renally Impaired Patients (CARE) Study: A Randomized Double-Blind Trial of Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease. *Circulation.* 2007 6 26;115(25):3189–96. [PubMed: 17562951]
17. Taliercio CP. Risks for Renal Dysfunction with Cardiac Angiography. *Ann Intern Med.* 1986 4 1;104(4):501. [PubMed: 3954277]
18. Moscucci M. Grossman & Baim's cardiac catheterization, angiography, and intervention. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2014
19. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. *AJR Am J Roentgenol.* 2004 12;183(6):1673–89. [PubMed: 15547209]

20. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med.* 1990 11;89(5):615–20. [PubMed: 2239981]
21. Freeman RV, O'Donnell M, Share D, Meengs WL, Kline-Rogers E, Clark VL, et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol.* 2002 11 15;90(10):1068–73. [PubMed: 12423705]
22. Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med.* 2009 2 3;150(3):170–7. [PubMed: 19189906]
23. Brown JR, Robb JF, Block CA, Schoolwerth AC, Kaplan AV, O'Connor GT, et al. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? *Circ Cardiovasc Interv.* 2010 8;3(4):346–50. [PubMed: 20587788]
24. Ogata N, Ikari Y, Nanasato M, Okutsu M, Kametani R, Abe M, et al. Safety margin of minimized contrast volume during percutaneous coronary intervention in patients with chronic kidney disease. *Cardiovasc Interv Ther.* 2014 7 1;29(3):209–15. [PubMed: 24474044]
25. Raposeiras-Roubín S, Abu-Assi E, Ocaranza-Sánchez R, Alvarez-Álvarez B, Cambeiro-González C, Fandiño-Vaquero R, et al. Dosing of iodinated contrast volume: a new simple algorithm to stratify the risk of contrast-induced nephropathy in patients with acute coronary syndrome. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* 2013 11 15;82(6):888–97.
26. Laskey WK, Jenkins C, Selzer F, Marroquin OC, Wilensky RL, Glaser R, et al. 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 8 14;50(7):584–90. [PubMed: 17692741]
27. Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, et al. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2011 8 23;58(9):907–14. [PubMed: 21851878]
28. Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. *Medicine (Baltimore).* 1979 5;58(3):270–9. [PubMed: 449662]
29. Heinrich MC, Häberle L, Müller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology.* 2009 1;250(1):68–86. [PubMed: 19092091]
30. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet Lond Engl.* 2015 6 20;385(9986):2465–76.
31. Andò G, Costa F, Trio O, Oreto G, Valgimigli M. Impact of vascular access on acute kidney injury after percutaneous coronary intervention. *Cardiovasc Revascularization Med Mol Interv.* 2016 8;17(5):333–8.
32. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004 10 6;44(7):1393–9. [PubMed: 15464318]
33. Brown JR, MacKenzie TA, Maddox TM, Fly J, Tsai TT, Plomondon ME, et al. Acute Kidney Injury Risk Prediction in Patients Undergoing Coronary Angiography in a National Veterans Health Administration Cohort With External Validation. *J Am Heart Assoc.* 2015 12 11;4(12).
34. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet Lond Engl.* 2010 12 18;376(9758):2096–103.
35. Rim MY, Ro H, Kang WC, Kim AJ, Park H, Chang JH, et al. The effect of renin-angiotensin-aldosterone system blockade on contrast-induced acute kidney injury: a propensity-matched study. *Am J Kidney Dis Off J Natl Kidney Found.* 2012 10;60(4):576–82.
36. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* 2012 2 15;79(3):453–95.

37. Acute Kidney Injury (AKI) – KDIGO [Internet]. [cited 2017 10 2]. Available from: <http://kdigo.org/guidelines/acute-kidney-injury/>
38. NQF: Safe Practices for Better Healthcare–2009 Update [Internet]. [cited 2017 10 2]. Available from: http://www.qualityforum.org/Publications/2009/03/Safe_Practices_for_Better_Healthcare%E2%80%932009_Update.aspx
39. CMS proposes IPPS changes for 2012 and beyond - www.hcpro.com [Internet]. [cited 2017 10 2]. Available from: <http://www.hcpro.com/HOM-265196-6962/CMS-proposes-IPPS-changes-for-2012-and-beyond.html>
40. Institute for Healthcare Improvement: Evidence-Based Care Bundles [Internet]. [cited 2017 9 19]. Available from: <http://www.ihl.org/Topics/Bundles/Pages/default.aspx>
41. Moscucci M, Rogers EK, Montoye C, Smith DE, Share D, O'Donnell M, et al. Association of a continuous quality improvement initiative with practice and outcome variations of contemporary percutaneous coronary interventions. *Circulation*. 2006 2 14;113(6):814–22. [PubMed: 16461821]
42. Brown JR, Solomon RJ, Sarnak MJ, McCullough PA, Splaine ME, Davies L, et al. Reducing contrast-induced acute kidney injury using a regional multicenter quality improvement intervention. *Circ Cardiovasc Qual Outcomes*. 2014 9;7(5):693–700. [PubMed: 25074372]
43. James MT, Ghali WA, Tonelli M, Faris P, Knudtson ML, Pannu N, et al. Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. *Kidney Int*. 2010 10;78(8):803–9. [PubMed: 20686453]

Figure 1:
Incidence rate of contrast-induced acute kidney injury (CI-AKI) according to whether the contrast media volume exceeded or did not exceed the maximum allowable contrast dose (MACD).

Figure 2:
Chemical structures of the benzene ring before and after tri-iodination.

Figure 3:

Two-step algorithm to stratify risk of contrast-induced acute kidney injury (CI-AKI) according to the maximal acceptable contrast dose (MACD) and the contrast volume to the estimated glomerular filtrate rate ratio (CV/eGFR). Modified from reference (25).

Table 1.

Classification of contrast media

Classification	Example	Comments	Iodine atoms per molecule	Molecular Structure	Osmotic particles/molecule	Contrast agent ratio *	MW (Da)	Osmolality (mOsm/L)
High-Osmolar Contrast Media (ionic)	Amidotrizoic acid (Urografin) Ioxitalamic acid (Telebrix®) Meglumine diatrizoate (Hypaque®), Cystografin® Sodium diatrizoate, meglumine diatrizoate (Renografin®) Iothalamate (Conray®) Metrizoate (Isopaque)	Oldest Cheapest Most nephrotoxic Most cardiotoxic ** (rare) Risk of extracellular fluid volume expansion	3	Monomers	2	1.5	600-800	1500-2076
Low-Osmolar Contrast Media (ionic)	Ioxaglate (Hexabrix®)	Less volume expansion	6	Dimer	2	3	1269	560
Low-Osmolar Contrast Media (nonionic)	Iohexol (Omnipaque®) Ioversol (Optiray®) Iopromide (Ultravist®) Iomeprol (Iomeron®) Iobitridol (Xenetix®) Iopamidol (Isovue-M®) Ioxilan (Oxilan®)	Less expensive Less nephrotoxic Less cardiotoxic Less anaphylaxis	3	Monomers	1	3	600-800	600-700
Iso-osmolar contrast media (nonionic)	Iodixanol (Visipaque®) Iotrolan (Osmovist®)	Most expensive Least cardiotoxic Least nephrotoxic	6	Dimers	1	6	1550-1626	290

* Contrast agent ratio = (number of iodine atoms)/ (number of particles in solution).

** Cardiac toxicity includes sinus bradycardia, heart block, shortness widening, QT prolongation, ST segment changes, angina T-wave inversion, ventricular tachycardia, and ventricular fibrillation.

Table 2.

Cohort studies examining the association between the maximum allowable contrast dose (MACD) and development of contrast-induced AKI.

Author (reference)	Year	Country	Study design	Sample size	Mean age, years	Prevalence of diabetes	Mean sCr or eGFR	Contrast media name (type)	Definition of CI-AKI	Prevent ative measures	Patients exceeding MACD	CI-AKI incidence rate		Odds ratio (95% CI) for CI- AKI (CV exceeding vs. not exceeding MACD)	Adjustment variables	Authors' conclusion	Study limitations
												CV not exceeding MACD	CV exceeding MACD				
Cigarroa et al.	1989	USA	Retrospective cohort	115	61	41.7%	2.6 mg/dL	Diatrizoate meglumine; sodium diatrizoate (HOCM)	1 mg/dL increase in sCr within 5 days	Normal saline	25%	2.0%	21.0%	-	-	CV should not exceed MACD to decrease risk of CI-AKI	Observational Small sample size Retrospective
Freeman et al.	2002	USA	Retrospective cohort	9,242	69	59.0%	> 2.0 mg/dL (2.8%)	Variable	Dialysis requirement	Not specified	11.6%	0.2%	2.4%	6.20 (3.00, 12.80)	Diabetes, pre-existing CKD, PVD, heart failure, cardiogenic shock	MACD, pre- existing CKD, diabetes, heart failure, and PVD are risk factors for dialysis- requiring CI- AKI	Observational
Moscucci et al.	2006	USA	Prospective	5901	63	30.2%	3.3% sCr< 2.0 mg/dL	Not specified	0.5 mg/dL increase in sCr	Pre-procedural hydration, intervention increasing awareness of CI- AKI according to MACD	5.9%	-	-			Quality improvement measures including less than MACD decrease the risk of CI- AKI and Dialysis- requiring AKI.	
Marenzi et al.	2009	Italy	Prospective cohort	561	62	14.0%	1.1 mg/dL	Iomeprol or iohexol (LOCM)	25% increase in sCr within 72 hours	Normal saline *	23.2%	13.0%	45.0%	-	-	CI-AKI risk and in- hospital mortality are closely associated with CV	Small sample Single center
Brown et al.	2010	USA	Prospective cohort	9,910	65	27.5%	75.8% eGFR> 60 ml/min/1.73m ²	Not specified (LOCM, 22%; IOCM, 78%)	0.3 mg/dL or 50% increase in sCr or dialysis requirement	Not specified	19.8%	5.9%	15.3%	CV/MACD ratio 1.0-1.5 = 1.60 (1.29, 1.97) CV/MACD ratio 1.5-2.0 = 2.02 (1.45, 2.81) CV/MACD ratio >2.0 = 2.94 (1.93, 4.48)	Age, sex, body surface area, baseline eGFR, diabetes, hypertension, heart failure, COPD, priority of PCI, number of stents inserted	Linear increase in CIN when exceeding MACD and risk increases regardless of baseline sCr	Observational Single Center
Ogata et al.	2013	Japan	Retrospective cohort	100	74	44.0%	22.8 mL/min/1.73m ²	Iomeprol, iopamidol iohexol, other (LOCM)	0.5 mg/dL or 25% increase in sCr within 48 hours	Not specified	35	11.0%	23.0%	-	-	Risk of CI- AKI increases when the CV exceeds the MACD	Observational Retrospective Small sample Selection bias

Author (reference)	Year	Country	Study design	Sample size	Mean age, years	Prevalence of diabetes	Mean sCr or eGFR	Contrast media name (type)	Definition of CI-AKI	Prevent ative measures	Patients exceeding MACD	CI-AKI incidence rate		Odds ratio (95% CI) for CI-AKI (CV exceeding vs. not exceeding MACD)	Adjustment variables	Authors' conclusion	Study limitations
												CV not exceeding MACD	CV exceeding MACD				
Raposeiras-Roubin et al.	2013	Spain	Retrospective cohort	940	67	23.4%	29.6% eGFR < 60 ml/min/1.73m ²	Non ionic (LOCM)	0.5 mg/dL increase in sCr within 72 hours	Normal saline **	Not specified	3.6%	36.1%	19.64 (9.81, 39.31)	-	Combining the CV/ MACD and CV/eGFR ratio increase the positive predictive value of a CI-AKI risk score (41% vs. 9%) with similar sensitivity (91% vs. 83%)	Observational Retrospective

MACD denotes Maximal Allowable Contrast Dose; CV, contrast volume; CI- AKI, contrast-induced acute kidney injury; OR, odds ratio; eGFR, estimated glomerular filtration rate; sCr, serum creatinine; CKD, chronic kidney disease;

HOCM, high-osmolar contrast media; LOCM, low-osmolar contrast media; IOCM, iso-osmolar contrast media; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease.

* Normal saline at 1 mL/kg/hour for 12 hours (0.5 mL/kg/hour if left ventricular ejection fraction <40%);

** Normal saline at 1mL/kg/hour started 3-12 hours before and continued to 24 hours after the procedure.

Table 3.

Preventative measures to reduce the risk of CI-AKI before, during and after cardiovascular procedures.

Before Procedure	During Procedure	After Procedure
<ul style="list-style-type: none"> - Oral hydration - Limit fasting state to 2-4 hours - Avoid nephrotoxic medications - Patients with pre-existing chronic kidney disease should be considered for early admission to ensure adequate hydration - Establish IV access for hydration as soon as possible - Document risk factors and plans to prevent CI-AKI - Calculate MACD or contrast volume to creatinine clearance or eGFR ratio to limit contrast volume 	<ul style="list-style-type: none"> - Continue IV hydration - Consider trans-radial approach - Select low- or iso-osmolar contrast agent - Use small catheters to limit contrast volume - Communicate to physician when MACD is about to be exceeded - Eliminate left ventriculography - Consider staging an intervention 	<ul style="list-style-type: none"> - Monitor kidney function for all patients - Continue IV and/or oral hydration