¹ Department of Cardiology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

² Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

Contrast-induced acute kidney injury

Lesão renal aguda induzida por contraste

Gustavo Neves de Araujo¹, Mateus Lech², Rodrigo Vugman Wainstein¹, Marco Vugman Wainstein¹

DOI: 10.31160/JOTCI2018;26(1)A0006

ABSTRACT – Contrast-induced acute kidney injury is not a rare event after exposure to contrast media, and affects approximately 1 to 2% of patients in general radiological imaging procedures. The incidence of contrast-induced acute kidney injury is even higher among patients undergoing percutaneous coronary intervention, and ranges from 3 to 19% according to the patient's risk profile. It is associated with increased morbidity, mortality, hospital length-of-stay and healthcare costs. Hence, since there is no targeted treatment after its onset, identifying high risk patients and preventing its occurrence is of paramount importance to avoid adverse outcomes after percutaneous coronary intervention.

Keywords: Contrast media; Acute kidney injury; Percutaneous coronary intervention

RESUMO – A lesão renal aguda induzida por contraste não é um evento raro após a exposição a este último e acomete cerca de 1 a 2% dos pacientes nos procedimentos radiológicos em geral. A incidência de lesão renal aguda induzida por contraste é ainda maior entre pacientes submetidos à intervenção coronária percutânea e varia de 3 a 19%, de acordo com o perfil de risco do paciente. Ela está associada a maior morbidade, mortalidade, tempo de hospitalização e custo de saúde. Como não existe tratamento específico após o estabelecimento do quadro, é muito importante identificar os pacientes de alto risco e prevenir a ocorrência dessa complicação, a fim de evitar desfechos adversos após a intervenção coronária percutânea.

Descritores: Meios de contraste; Lesão renal aguda; Intervenção coronária percutânea

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is not a rare event after exposure to contrast media, and affects roughly 1 to 2% of patients in general radiological imaging procedures.¹ CI-AKI incidence is even higher among patients undergoing percutaneous coronary intervention (PCI), and ranges from 3 to 19% according to the patient's risk profile.²⁻⁴ CI-AKI is associated with increased morbidity, mortality, hospital length-of-stay and healthcare costs.⁴ Hence, since there is no targeted treatment after its onset, identifying high risk patients and preventing its occurrence is of paramount importance to avoid adverse outcomes after PCI. Summarized information on CI-AKI is shown in figure 1.

How to cite this article:

Araujo GN, Lech M, Wainstein RV, Wainstein MV. Contrast-induced acute kidney injury. J Transcat Intervent. 2018;26(1):eA0006. [https://doi.org/10.31160/JOTCI2018;26\(1\)A0006](https://doi.org/10.31160/JOTCI2018;26(1)A0006)

Corresponding author:

Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2.350 – Santana
Zip code: 04311-050 – Porto Alegre, RS, Brazil
E-mail: gustavon.araujo@gmail.com

Received in:

March 3, 2018

Accepted in:

October 31, 2018

This content is licensed under a Creative Commons Attribution 4.0 International License.

Definition
A rise of 0.3mg/dL or 50% in 48 to 72 hours post-procedure creatinine compared to baseline
Pathophysiology
Afferent vasoconstriction and direct tubular damage
Risk factors
Related to previous kidney perfusion and nephrotoxicity
Clinical implications
Increased risk of bleeding, dialysis, stroke, myocardial infarction and mortality
Prevention
Identify high risk patients, avoid high volume of contrast, hydration protocols, avoid concomitant nephrotoxic agents

Figure 1. Summarized information on contrast-induced acute kidney injury.

PATHOPHYSIOLOGY

The pathophysiology of contrast-induced nephropathy (CIN) is complex, multifactorial and only partially understood (Figure 2). The implicated mechanisms are associated with afferent arterioles vasoconstriction and direct tubular damage caused by iodinated contrast media (ICM), but some clinical aspects, such as hemodynamic instability, cholesterol embolism to the kidney, and concomitant drug toxicity can potentiate CIN development and severity.

Iodinated contrast media are water soluble carbon-based benzene rings used in interventional radiology to obtain vessel and chamber imaging. ICM causes a direct toxic effect on renal tubular cells by exposing them to high osmotic load, inducing impairment in intracellular transport and energy metabolism, and leading to cytopathological changes ranging from tubular cell vacuolisation to necrosis.⁵ Increased renal interstitial pressure after exposure to contrast media also plays a role in the pathophysiology of CIN, since raised interstitial pressure may compress the microcirculation of the vasa recta, resulting in medullary hypoxia and CIN.⁶

When iodinated contrast is injected into the systemic arterial circuit, there is a transient endothelium-dependent vasodilation mediated by release of nitric oxide (NO), followed by arteriolar vasoconstriction, lasting from seconds to hours. NO causes a release of reactive oxygen species, leading to a reduction in partial pressure of arterial

oxygen (PaO_2) and increased vascular reactivity to various vasoconstrictors, such as norepinephrine, angiotensin II, endothelin and adenosine. In humans, total renal blood flow may be reduced by up to 50% after the injection of ICM.⁷ The persistent decline in glomerular filtration that follows ICM administration also results in an increased generation of reactive oxygen species.⁸

The reduction in renal blood flow affects particularly the outer medulla, which is more susceptible to ischemia and apoptosis of the tubular cells due to its high metabolic activity. Since there is no glomerular injury, hematuria is not present. Oliguria is also not expected in CI-AKI. Subclinical kidney injury occurs in virtually every patient exposed to iodinated contrast; however, because there is a robust tubular repair capability in healthy subjects, clinically relevant CI-AKI only occurs in predisposed patients who are unable to rapidly repair tubular damage.

A less common cause of kidney injury after PCI is cholesterol embolism. Considering that the kidneys receive 25% of cardiac output, microshowers of atheroembolic material may deposit in the renal tissue after PCI. Cholesterol embolization syndrome (affecting different organs) occurs in up to 1.4% of patients undergoing cardiac catheterization.⁹ However, a series of autopsies in patients who died within 6 months after arteriography procedures showed that subclinical embolization can be seen in up to 30% of cases.¹⁰

Figure 2. Pathophysiology of contrast-induced acute kidney injury in patients with and/or without myocardial infarction.

DEFINITION AND DIAGNOSIS

The most contemporary CI-AKI definition is a rise of 0.3mg/dL or 50% in creatinine, 48 to 72 hours after the procedure, as compared to baseline values. The increase in post-procedure creatinine, however, has been controversial. Definitions range from a more restrictive (i.e., an increase >1.0mg/dL in creatinine above baseline) to a more sensitive criteria (i.e., an increase of creatinine > 25% above baseline), which leads to a wide variation in its incidence (2% in restrictive¹¹ and 12.3% in sensitive criteria¹²), and short- and long-term prognostic value after CI-AKI development. Harjai et al.¹³ compared different definitions of CI-AKI, and found that a more restrictive criteria fails to identify a large amount of patients with smaller increases in creatinine, leading to underestimation of the incidence of CI-AKI and failing to predict adverse events. In this study, a rise in serum creatinine ≥ 0.5 mg/dL and/or $\geq 25\%$ within 72 hours after PCI was predictive of 6-month major adverse cardiovascular events (MACE) and all-cause mortality after PCI. Although several studies used the latter definition,^{14,15} growing data suggested that CI-AKI identification could be improved.

In 2007, the Acute Kidney Injury Network (AKIN) suggested a novel CI-AKI definition in order to standardize AKI assessment and classification in everyday clinical practice, as well as in research conditions.¹⁶ CI-AKI was defined as a rise of creatinine 48 to 72 hours after procedure higher than 0.3mg/dL or 50% compared to baseline. The absolute criteria for the diagnosis of CI-AKI were based on the emerging knowledge that even small variations in creatinine levels are associated with higher morbidity and mortality rates. Centola et al. confirmed that AKIN definition provides a better accuracy in predicting long-term mortality compared to a rise in serum creatinine ≥ 0.5 mg/dL and/or $\geq 25\%$ within 72 hours after PCI.¹⁷ Using a definition that correlates better with hard outcomes seems reasonable, since reducing CI-AKI may potentially reduce these outcomes.

EPIDEMIOLOGY

The incidence of CI-AKI is highly variable in literature. It depends on procedure type, contrast load, clinical presentation (i.e. primary vs. elective PCI), population characteristics and CI-AKI definition, which is not uniform, as commented.

In hospitalized patients, contrast medium exposure after radiological imaging procedures is related to the development of acute kidney injury in approximately 1% of cases.¹ According to the National Cardiovascular Data Registry (NCDR®), 7.1% of 985,737 patients undergoing elective and urgent PCI developed CI-AKI (AKIN definition), and 0.3% (n=3005) required new dialysis.¹⁸ While CI-AKI was complicated in 4.4% of elective cases, it was observed in 7.9% of patients after acute coronary syndromes, in 10.9% of patients after ST-elevation myocardial infarction

(STEMI) and in 36.9% of chronic renal disease (CKD) patients presenting with STEMI. In an Italian registry, the incidence of CI-AKI was 14% in patients hospitalized with acute coronary syndromes;¹⁹ the same authors had previously found an incidence of 19% using a different CI-AKI definition.²

RISK FACTORS

The risk factors for CI-AKI are mainly related to previous kidney dysfunction, current nephrotoxicity and potential kidney malperfusion, and can be classified into modifiable and non-modifiable risk factors (Chart 1). Patients with pre-existing kidney disease are unable to rapidly correct tubular damage, potentially leading to CI-AKI. CI-AKI risk is directly related to baseline glomerular filtration rate (Table 1).¹⁸ Age is a risk due to natural loss of tubular function, but also because of more difficult vascular access requiring greater amount of contrast, presence of multivessel disease, and comorbidities. Diabetic patients more often present renal dysfunction, as well as a higher risk of vascular disease. Anemia leads to reduced kidney perfusion, and to cardiac risk factors, such as heart failure, cardiogenic shock and use of intra-aortic balloon pump. Acute coronary syndromes increase the risk of CI-AKI due to a multifactorial mechanism, including kidney damage by inflammatory cytokines and kidney hypoperfusion. Use of other nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs, also increase the risk of CI-AKI.

Contrast media is nephrotoxic, thus the risk of CI-AKI is dose-related. However, CI-AKI is unlikely in patients receiving less than 100mL of volume.²⁰ Increasing complexity of coronary intervention leads to higher volumes of contrast,

Chart 1. Risk factors for development of contrast-induced acute kidney injury.

Non-modifiable	Modifiable
Age	Anemia
Heart failure	Contrast volume
Diabetes mellitus	Contrast osmolality*
Acute coronary syndromes	Cardiogenic shock
Pre-existing kidney disease	Nephrotoxic medications

* Iso-osmolar and low-osmolar contrast appear to reduce the risk of contrast nephropathy.

Table 1. Contrast-induced acute kidney injury (CI-AKI) risk according to glomerular filtration rate

Glomerular filtration rate mL/minute	CI-AKI risk (%)
>60	5.2
60-45	8.0
45-30	12.9
<30	26.6

leading to increased risk of CI-AKI. Contrast osmolality plays an important role in the development of CI-AKI. High-osmolar contrast media (HOCM) allow a good vascular opacification, but are more often associated with allergic reactions, and have a higher rate of CIN as compared to low-osmolar contrast media (LOCM), especially in high risk patients.²¹ Since LOCM still have higher osmolality than blood (890mosmol/L vs. 290mosmol/L), the advent of iso-osmolar contrast media (IOCM; iso-osmolar compared to blood) was further promising, but a systematic review of 17 trials, with 1,365 high-risk patients, showed that the risk of CI-AKI was similar using IOCM and LOCM.²²

The incidence of CI-AKI with iohexol (low-osmolar) is higher than with iopamidol (low-osmolar) and iodixanol (iso-osmolar), while there is no difference between the latter two agents. This shows that although osmolality might play a key role in kidney damage, other factors, such as viscosity and ionicity, are also involved. Increased plasma viscosity directly impairs blood flow to the renal medulla by vascular and tubular mechanisms, and it is believed that IOCM (which have higher viscosity than both LOCM and HOCM) do not reduce the incidence of CI-AKI compared to LOCM. Ionic agents are more related to allergic reactions. As described above, HOCM (which are always ionic) are more related to this complication. When ioxaglate (ionic LOCM) and iodixanol (non-ionic IOCM) were compared, hypersensitivity reactions occurred in 2.5% vs. 0.7% of patients ($p=0.007$).²³

CLINICAL IMPLICATIONS

The most common manifestation of CI-AKI is an asymptomatic transient decline in renal function, which starts within 24 hours of procedure, has a peak in 3 to 5 days, and returns to baseline within 14 days. Approximately 1% of patients who develop CI-AKI may require hemodialysis due to oliguric renal failure, volume overload and hyperkalemia; of those, up to one fourth (0.23%) will require permanent dialysis or kidney transplantation.²⁴

CI-AKI is associated with higher rates of access-site complications, including bleeding, hematoma and pseudoaneurysms.⁴ Non-cardiac complications, such as stroke, pulmonary embolism and gastrointestinal hemorrhage are also more common. The length of hospital stay in patients with CI-AKI is approximately 1.5 fold longer than in patients with no CI-AKI.^{2,25} Acute renal failure requiring dialysis after PCI is a particularly severe complication associated with in-hospital mortality rate of 27%.²⁴ The in-hospital rate of myocardial infarction is approximately 4% in patients who develop CI-AKI, compared to 2% in patients who do not present such condition. The rates of myocardial infarction are even higher (7.9%) in patients who require dialysis.¹⁸

Both in-hospital and long-term mortality are higher in patients who develop CI-AKI (Figure 3). These findings are consistent throughout the literature, with follow-up

periods as long as 5 years.^{4,14, 8,26,27} However, since all data available are based in observational studies, researchers have recently questioned the true impact of CI-AKI in hard outcomes, suggesting that it is only a marker of high risk patients who developed clinical events despite of CI-AKI.^{25,28} Acute kidney injury is strongly associated with important risk factors for mortality, such as preexisting CKD, diabetes, left ventricular dysfunction and markers of more aggressive atherosclerosis (i.e. cerebrovascular disease). Moreover, it is curious to see how a transient decrease in glomerular filtration rate (GFR), with total recovery within a few days, can be associated with such an increase in mortality. On the other hand, it is possible that acute tubular injury triggers clinical events in other organs with mechanisms still not completely understood. Yet, it is of great importance trying to anticipate CI-AKI while this doubt remains unsolved. Defining the association of AKI with an adverse long-term prognosis identifies a high-risk cohort that warrants aggressive secondary prevention and monitoring.

Figure 3. Risk of death, bleeding and myocardial infarction (MI) in patients with and without contrast-induced acute kidney injury (CI-AKI). Source: Adapted from Tsai et al.¹⁸

TREATMENT

There is no specific treatment for CI-AKI. Thus, the main strategy to avoid it lies on prevention and identification of high-risk patients. Multiple prediction models have been created in different populations using discrepant CI-AKI definitions.^{11,15,29-32} Given the distinct clinical characteristics of each population, these models perform well where they were developed, but may not predict CI-AKI so effectively in different scenarios. Mehran risk score¹⁵ is the most commonly used predictive model, and includes eight variables (hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age >75 years, anemia, and contrast volume) with a cumulative score dividing patients from low (7.5%) to very high risk (57.3%) of developing CI-AKI. When compared to another widely used risk model in a population from northwest

USA undergoing elective or urgent PCI, Mehran risk score was found to predict CI-AKI³³ more accurately. When compared to ACEF-MDRD score in a population from southern Brazil undergoing primary PCI, Mehran risk score was less accurate.³⁴ ACEF-MDRD score had an excellent negative predictive value (92.6%; 95%CI: 88.9-95.4%), and had the advantage of using only three variables to be calculated. Ideally, each population should have their own risk prediction tool.

The management principles include minimization of the total amount of contrast (i.e. biplane coronary angiography, “staged” procedures, avoid ventriculography) and routine use of hydration protocols before contrast exposure.³⁵ Volume expansion inhibits the renin-angiotensin system, dilutes the contrast media, and protects against reactive oxygen species.³⁶ Administration of iso- or low-osmolar rather than high-osmolar contrast media is also recommended,²² as well as avoiding use of concomitant nephrotoxic agents. Figure 4 shows a flowchart of suggested management of CI-AKI according to baseline risk factors.

Hydration is the cornerstone for prevention of CI-AKI, by increasing renal flow, reducing the contraction of renal vessels and diluting direct nephrotoxic agents. Only intravenous hydration with isotonic sodium chloride is uniformly accepted in clinical practice, with consistent evidence of its effectiveness in reducing CI-AKI.³⁷⁻³⁹ Although there is a recent article questioning the true impact of hydration in preventing CI-AKI,⁴⁰ the patients in this study had very low risk of developing CI-AKI, and risk reduction

could not be observed. In such patients, oral hydration is at least as effective as intravenous hydration.⁴¹

Excessive hydration and volume overload, however, may be deleterious and increase CI-AKI risk,⁴² probably due to increased afterload, similar to what occurs in cardiorenal syndrome. In order to guarantee an euvolemic state, hemodynamic-guided hydration have been tested and proved to reduce CI-AKI incidence in patients with heart failure and/or chronic kidney disease. Central venous pressure⁴³ and left ventricular end-diastolic pressure⁴⁴ were the strategies used to guide hydration.

Sodium bicarbonate hydration is not more effective than sodium chloride volume expansion, but has the advantage of using less volume when volume overload is not desired (i.e. patients with heart failure). While sodium chloride protocols recommend an infusion of 1mL/kg body weight per hour, 12 hours before and 12 hours after administration of the contrast agent, a widely-used sodium bicarbonate protocol⁴⁵ consists of 3mL/kg body weight for 1 hour before, and 1mL/kg during contrast exposure, and for 6 hours after the procedure. There are at least six meta-analyses⁴⁶⁻⁵⁰ comparing sodium bicarbonate and sodium chloride (among other strategies), showing conflicting results. The ones favoring sodium bicarbonate were performed in higher risk patients and with higher event rate. One of the studies⁴⁸ showed a reduction in mortality with sodium bicarbonate (hazard ratio 0.61; 95%CI 0.41-0.89; $p=0.011$), although there was a statistically significant interaction between the effect on mortality and the occurrence of

Figure 4. Flowchart of suggested management of contrast-induced acute kidney injury, according to baseline risk factors. GFR: glomerular filtration rate.

CI-AKI. A recent randomized controlled trial including 4,993 high-risk patients did not show benefit of intravenous sodium bicarbonate over intravenous sodium chloride for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days.⁵¹

High volumes of crystalloid infusion with forced diuresis (RenalGuard system®) were compared with sodium bicarbonate, and were found to reduce the incidence of CI-AKI in high-risk patients submitted to PCI and transcatheter aortic valve replacement (TAVR).^{52,53} RenalGuard® measures and controls intravenous crystalloid volume with urine output, increasing the urine flow rate (>150mL/hour) and reducing the toxic effect of contrast medium. The device, however, is not widely available and its use has not been very popular.

Statins are the only pharmacological intervention to date that consistently prevents CI-AKI, probably through their pleiotropic effect on inflammatory pathways, endothelial reactivity, and apoptosis. Statins reduce the incidence of CI-AKI irrespective of the presence of diabetes and CKD.⁵⁴ However, one can argue that while statins are known to reduce the incidence of other cardiovascular outcomes it can also consequently decrease the incidence of CI-AKI.

Other pharmacological therapies remain controversial. There have been small randomized trials showing benefit from agents, such as theophylline, trimetazidine and ascorbic acid, among others;⁵⁵⁻⁵⁹ however, because of the small benefit and the inconsistent results in larger randomized trials, there is currently no conclusive evidence to broadly use any of these medications. Acetylcysteine is an illustrative example of a medication that performed well in small trials and even in a meta-analysis,⁵⁰ but failed to reduce CI-AKI risk in a well-designed large randomized trial of 2308 patients.⁵⁶

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the incidence of CI-AKI and should be avoided.⁶⁰ By reducing intraglomerular pressure due to efferent arteriolar dilation, they may cause loss of ability to raise intraglomerular pressure to maintain glomerular filtration and forward flow of urine through the proximal tubules and the remainder of the nephron.

CONCLUSION

Contrast-induced acute kidney injury is a common complication in patients receiving iodinated contrasts, and even more common in patients with ST-elevation myocardial infarction submitted to invasive cardiac interventions. The lack of effective treatment strategies once contrast-induced acute kidney injury develops, in conjunction with the demonstrated long-term risks associated with the development of contrast-induced acute kidney injury, make identification of high-risk patients and targeted implementation of contrast-induced acute kidney injury preventative strategies be the best contemporary approach to avoid harmful effects associated with contrast-induced acute kidney injury.

FINANCING

None.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

REFERENCES

- Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* 2002;39(5):930-6.
- Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, et al. Contrast-induced acute kidney injury in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 2004;44(9):1780-5.
- Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med.* 1998;128(3):194-203.
- Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002;105(19):2259-64.
- Tervahartiala P, Kivisaari L, Kivisaari R, Vehmas T, Virtanen I. Structural changes in the renal proximal tubular cells induced by iodinated contrast media. *Nephron.* 1997;76(1):96-102.
- Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int.* 2005;68(1):14-22.
- Tumlin J, Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA; CIN Consensus Working Panel. Pathophysiology of contrast-induced nephropathy. *Am J Cardiol.* 2006;98(6A):14K-20K.
- Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radioccontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol.* 1990;258(1 Pt 2):F115-20.
- Fukumoto Y, Tsutsui H, Tsuchihashi M, Masumoto A, Takeshita A; Cholesterol Embolism Study(CHEST) Investigators. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. *J Am Coll Cardiol.* 2003;42(2):211-6.
- Ramirez G, O'Neill WM Jr., Lambert R, Bloomer HA. Cholesterol embolization: a complication of angiography. *Arch Intern Med.* 1978;138(9):1430-2.
- Bartholomew BA, Harjai KJ, Dukupati S, Boura JA, Yerkey MW, Glazier S, et al. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol.* 2004;93(12):1515-9.
- Crimi G, Leonardi S, Costa F, Ariotti S, Tebaldi M, Biscaglia S, et al. Incidence, prognostic impact, and optimal definition of contrast-induced acute kidney injury in consecutive patients with stable or unstable coronary artery disease undergoing percutaneous coronary intervention. insights from the all-comer PRODIGY trial. *Catheter Cardiovasc Interv.* 2015;86(1):E19-27.
- Harjai KJ, Raizada A, Shenoy C, Sattur S, Orshaw P, Yaeger K, et al. A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. *Am J Cardiol.* 2008;101(6):812-9.
- Narula A, Mehran R, Weisz G, Dangas GD, Yu J, Gnreux P, et al. Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy. *Eur Heart J.* 2014;35(23):1533-40.

15. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of Contrast-induced acute kidney injury after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004;44(7):1393-9.
16. Ad-hoc working group of ERBP, Fliser D, Laville M, Covic A, Fouque D, Vanholder R, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant.* 2012; 27(12):4263-72.
17. Centola M, Lucuzziotti S, Salerno-Uriarte D, Sponzilli C, Ferrante G, Acquaviva R, et al. A comparison between two different definitions of contrast-induced acute kidney injury in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Int J Cardiol.* 2016; 210:4-9.
18. 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;7(1):1-9.
19. Marenzi G, Cabiati A, Bertoli SV, Assanelli E, Marana I, De Metrio M, et al. Incidence and relevance of acute kidney injury in patients hospitalized with acute coronary syndromes. *Am J Cardiol.* 2013;111(6):816-22.
20. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med.* 1997;103(5):368-75.
21. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology.* 1993;188(1):171-8.
22. Solomon R. The role of osmolality in the incidence of Contrast-induced acute kidney injury: a systematic review of angiographic contrast media in high risk patients. *Kidney Int.* 2005;68(5):2256-63.
23. Bertrand ME, Esplugas E, Piessens J, Rasch W. Influence of a non-ionic, iso-osmolar contrast medium (iodixanol) versus a ionic, low-osmolar contrast medium (ioxiglate) on major adverse cardiac events in patients undergoing percutaneous transluminal coronary angioplasty: a multicenter, randomized double-blind study. *Circulation.* 2000;101(2):131-6.
24. Gruberg L, Mehran R, Dangas G, Mintz GS, Waksman R, Kent KM, et al. Acute renal failure requiring dialysis after percutaneous coronary interventions. *Catheter Cardiovasc Interv.* 2001;52(4):409-16.
25. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, et al. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circ Cardiovasc Interv.* 2013;6(1):37-43.
26. Amin AP, Spertus JA, Reid KJ, Lan X, Buchanan DM, Decker C, et al. The prognostic importance of worsening renal function during an acute myocardial infarction on long-term mortality. *Am Heart J.* 2010;160(6):1065-71.
27. Goldberg A, Hammerman H, Petcherski S, Zdoroviyak A, Yalonsky S, Kapeliovich M, et al. In-hospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J.* 2005;150(2):330-7.
28. Silvain J, Collet JP, Montalescot G. Contrast-induced acute kidney injury: the sin of primary percutaneous coronary intervention? *Eur Heart J.* 2014;35(23):1504-6.
29. 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;4(12). pii: e002136.
30. Tziakas D, Chalikias G, Stakos D, Apostolakis S, Adina T, Kikas P, et al. Development of an easily applicable risk score model for Contrast-induced acute kidney injury prediction after percutaneous coronary intervention: a novel approach tailored to current practice. *Int J Cardiol.* 2013;163(1):46-55.
31. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* 2013; 61(22):2242-8.
32. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc.* 2014;3(6):e001380.
33. Araujo GN, Wainstein MV, McCabe JM, Huang PH, Govindarajulu US, Resnic FS. Comparison of two risk models in predicting the incidence of contrast-induced acute kidney injury after percutaneous coronary intervention. *J Interv Cardiol.* 2016;29(5):447-53.
34. Araujo GN, Pivatto Junior F, Fuhr B, Cassol EP, Machado GP, Valle FH, et al. Simplifying contrast-induced acute kidney injury prediction after primary percutaneous coronary intervention: the age, creatinine and ejection fraction score. *Cardiovasc Interv Ther.* 2018;33(3):224-31.
35. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35(37):2541-619.
36. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest.* 1998;114(6):1570-4.
37. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med.* 1994;331(21):1416-20.
38. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med.* 2002;162(3):329-36.
39. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract.* 2003;93(1):C29-34.
40. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of Contrast-induced acute kidney injury (AMACI-AKIG): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet.* 2017;389(10076):1312-22.
41. Agarwal SK, Mohareb S, Patel A, Yacoub R, DiNicolantonio JJ, Konstantinidis I, et al. Systematic oral hydration with water is similar to parenteral hydration for prevention of Contrast-induced acute kidney injury: an updated meta-analysis of randomised clinical data. *Open Heart.* 2015;2(1):e000317.
42. Liu Y, Li H, Chen S, Chen J, Tan N, Zhou Y, et al. Excessively high hydration volume may not be associated with decreased risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with renal insufficiency. *J Am Heart Assoc.* 2016;5(6). pii: e003171.

43. Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced acute kidney injury by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. *JACC Cardiovasc Interv.* 2016;9(1):89-96.
44. Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet.* 2014;383(9931):1814-23.
45. Briguori C, Airolidi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation.* 2007;115(10):1211-7.
46. Ali-Hasan-Al-Saegh S, Mirhosseini SJ, GhodratiPour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, et al. Strategies preventing contrast-induced nephropathy after coronary angiography: a comprehensive meta-analysis and systematic review of 125 randomized controlled trials. *Angiology.* 2017;68(5):389-413.
47. Su X, Xie X, Liu L, Lv J, Song F, Perkovic V, et al. Comparative effectiveness of 12 treatment strategies for preventing contrast-induced acute kidney injury: a systematic review and bayesian network meta-analysis. *Am J Kidney Dis.* 2017;69(1):69-77.
48. Brown JR, Pearlman DM, Marshall EJ, Alam SS, MacKenzie TA, Recio-Mayoral A, et al. Meta-analysis of individual patient data of sodium bicarbonate and sodium chloride for all-cause mortality after coronary angiography. *Am J Cardiol.* 2016;118(10):1473-9.
49. Zhao SJ, Zhong ZS, Qi GX, Tian W. The efficacy of N-acetylcysteine plus sodium bicarbonate in the prevention of contrast-induced nephropathy after cardiac catheterization and percutaneous coronary intervention: A meta-analysis of randomized controlled trials. *Int J Cardiol.* 2016;221:251-9.
50. 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;164(6):406-16.
51. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, Conner TA, Chertow GM, Bhatt DL, Shunk K, Parikh CR, McFalls EO, Brophy M, Ferguson R, Wu H, Androsenko M, Myles J, Kaufman J, Palevsky PM; PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med.* 2018;378(7):603-14.
52. Zhang B, Liang L, Chen W, Liang C, Zhang S. The efficacy of sodium bicarbonate in preventing Contrast-induced acute kidney injury in patients with pre-existing renal insufficiency: a meta-analysis. *BMJ Open.* 2015;5(3):e006989.
53. Solomon R. Forced diuresis with the RenalGuard system: impact on contrast induced acute kidney injury. *J Cardiol.* 2014;63(1):9-13.
54. Barbanti M, Gulino S, Capranzano P, Imme S, Sgroi C, Tamburino C, et al. Acute kidney injury with the renalguard system in patients undergoing transcatheter aortic valve replacement: The PROTECT-TAVI Trial (PROphylactic effect of furosemide-induced diuresis with matched isotonic intravenous hydration in transcatheter aortic valve implantation). *JACC Cardiovasc Interv.* 2015;8(12):1595-604.
55. Ukaigwe A, Karmacharya P, Mahmood M, Pathak R, Aryal MR, Jalota L, et al. Meta-analysis on efficacy of statins for prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography. *Am J Cardiol.* 2014;114(9):1295-302.
56. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced acute kidney injury Trial (ACT). *Circulation.* 2011;124(11):1250-9.
57. Nadkarni GN, Konstantinidis I, Patel A, Yacoub R, Kumbala D, Patel RA, et al. Trimetazidine decreases risk of contrast-induced acute kidney injury in patients with chronic kidney disease: A meta-analysis of randomized controlled trials. *J Cardiovasc Pharmacol Ther.* 2015;20(6):539-46.
58. Sadat U, Usman A, Gillard JH, Boyle JR. Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography: a systematic review with meta-analysis of randomized, controlled trials. *J Am Coll Cardiol.* 2013;62(23):2167-75.
59. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced acute kidney injury. *Ann Intern Med.* 2008;148(4):284-94. Erratum in: *Ann Intern Med.* 2008;149(3):219.
60. Bainey KR, Rahim S, Etherington K, Rokoss ML, Natarajan MK, Velianou JL, Brons S, Mehta SR; CAPTAIN Investigators. Effects of withdrawing vs continuing renin-angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: Results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial. *Am Heart J.* 2015;170(1):110-6.