Because of the increased use of contrast media, the potential risk of contrast-induced acute kidney injury (CIAKI) has also increased. CIAKI often results in chronic kidney disease (CKD), an affliction with increasing incidence in modern society. The current prevalence of CIAKI is difficult to estimate because most victims are asymptomatic. The first Japanese guidelines regarding contrast agent examinations were recently announced, but their only recommendation is to provide classic fluid replacement with saline 6–12 h before and after the contrast procedure. According to a review summarizing the recent literature, little evidence supports this suggestion. To obtain early diagnoses and to treat emergent patients, it is appropriate to perform procedures using contrast media without knowledge of patients’ renal function. Prevention of CIAKI is the most important consideration, and the usefulness of risk scores predicting the development of CIAKI has been reported. However, no prospective studies have been performed to date, and, therefore, such studies will be necessary in the future. Furthermore, the development of novel preventative interventions for CIAKI is also required. (doi: 10.2302/kjm.2015-0013-IR; Keio J Med 65 (4) : 67–73, December 2016)

**Keywords:** contrast-induced acute kidney injury, chronic kidney disease, risk factor, cholesterol embolism, biomarkers

**Introduction**

In recent years, the ageing of the population has led to an increase in the frequency of tests that use contrast medium. Normally, CIAKI resolves without accompanying oliguria, but some patients require blood purification therapy or develop irreversible renal failure. Particularly in emergency care facilities, tests and treatments utilizing contrast media must be performed on patients with a high risk of developing CIAKI, so it is essential that medical professionals understand the characteristics of CIAKI and the relevant preventative measures.

**Defining CIAKI**

The current widely used definition of CIAKI, according to the European Society of Urogenital Radiology (ESUR), is “a renal disorder occurring within 3 days after intravascular administration of a contrast agent, in the absence of any other etiology, and in which serum creatinine levels are elevated by 25% or more, or show elevated levels of 0.5 mg/dl or higher.”

ESUR continuously consolidates and examines new knowledge and continues to revise the guidelines.

The term CIAKI is widely used in the literature and is usually defined as a rise in serum creatinine of ≥ 0.5 mg/dl or a 25% increase from the baseline value assessed at 48 h after a radiological procedure. In 2012 a joint effort by the Japanese Society of Nephrology, the Japan Radiological Society, and the Japanese Circulation Society resulted in the country’s first guidelines for CIAKI. These guidelines defined CIAKI in a similar way to the ESUR guidelines as an increase in serum creatinine level of at least 0.5 mg/dl or 25% over the pre-administration level occurring within 72 h after the administration of an iodine contrast agent. Although CIAKI is a form of acute
kidney injury (AKI), it is not generally accompanied by oliguria. Consequently, urinary output is not included among the criteria. Because there was no established definition of CIAKI in Japan prior to the creation of these guidelines, the clinical study of the issues associated with CIAKI can be expected to increase in the future.

**Mechanism of Renal Injury**

After the administration of contrast agent, the secretion of endothelin and other vasoconstrictive peptides derived from vascular endothelial cells is promoted in the renal parenchyma. Consequent vasospasms cause a decline in the renal blood flow and oxygen supply. Additionally, the amount of NaCl that reaches the ascending limb of the loop of Henlé increases as a result of the osmotic activity caused by the contrast medium. As the amount of reabsorbed increases, oxygen demand and consumption also increase. This causes the kidney medulla to suffer hypoxia, which in turn causes damage to the parenchyma because of the increased production of free radicals by tubular epithelial cells. Moreover, the concentration of the contrast medium flowing through the renal tubule lumen gradually increases to such high levels that the toxicity of the contrast medium itself is thought to cause direct damage to tubular epithelial cells.

**Risk Factors**

Representative risk factors for CIAKI are shown in Table 1. The most important risk factor is pre-existing CKD. In fact, many recent studies no longer consider diseases such as diabetes and multiple myeloma to be risk factors if they are not accompanied by CKD. McCullough reported that decreased renal function leads to increased incidence of CIAKI. The ESUR Contrast Media Safety Committee’s guidelines, released in 2011, indicate that the CIAKI onset risk threshold for intravenous contrast administration is a glomerular filtration rate (GFR) of 45 mL/min/1.73 m². Thus, it is advisable to implement the preventative measures mentioned below when administering contrast medium to patients with risk factors. Cigarroa et al. previously calculated the maximal doses of contrast agents based on body weight and serum creatinine levels and reported that the incidence of CIAKI resulting from the administration of contrast agents at doses exceeding the maximum limit was 21%, which was significantly higher than the 2% incidence found with the administration of contrast agents within the limits of maximum authorized doses.

No definitive conclusion has yet been reached on whether the risk of developing CIAKI differs between iso-osmolar contrast media and low-osmolar contrast media. In addition, there is currently no evidence that intra-arterial injection of contrast medium is an independent risk factor for developing CIAKI; however, the incidence of CIAKI associated with intravenous administration of contrast media tends to be lower than that associated with intra-arterial administration. Therefore, if the benefit of using contrast medium in patients who have the risk factors listed in Table 2 outweighs the risk of CIAKI, the use of contrast medium should be considered.

Care is also required when carrying out contrast medium procedures on patients currently taking insulin sensitizers such as biguanide because of the risk of lactic acidosis associated with CIAKI onset. Although lactic acidosis is rare, once it develops, prognosis is poor and the mortality rate is high. It is recommended that such patients cease taking insulin-sensitizing medication 2 days prior to and 2 days following tests involving contrast medium.

The effectiveness of risk scores for CIAKI onset in patients undergoing percutaneous coronary intervention (PCI) has been reported; these data are described in Tables 2, 3. However, since prospective studies on this subject have not yet been conducted, it is not currently possible to make recommendations based on these data.

**Prevalence and Mortality**

Reports on the prevalence of CIAKI vary, but Kim et al. reported the prevalence of CIAKI after contrast-
enhanced CT as 0% for patients with eGFR 45–59 mL/min/1.73 m², 2.9% for eGFR 30–44 mL/min/1.73 m², and 12.1% for eGFR < 30 mL/min/1.73 m².

Most patients who undergo contrast-enhanced CT do so as outpatients, which makes it difficult to assess post-procedure renal function. However, reports indicate that approximately 12% of outpatients who undergo contrast-enhanced CT later develop CIAKI after returning home.\textsuperscript{15} An investigation of patients hospitalized in our medical department indicated that 9% of hospitalized patients who underwent procedures involving contrast medium developed CIAKI.\textsuperscript{16} This issue requires further study. Overestimation of the prevalence of CIAKI is also a subject of debate.\textsuperscript{17}

Although the 5-year survival rate is 90% in cases of reversible CIAKI resulting from coronary arteriography carried out on CKD patients, for irreversible cases, the 5-year survival rate is 32%.\textsuperscript{18} In addition, in a study of patients who underwent PCI, the total mortality rate after 1 year for patients who did not develop CIAKI was 19.4%, which was significantly lower than the 37.7% rate for those who did develop CIAKI.\textsuperscript{19} Another report indicated that among patients who underwent PCI, the in-hospital mortality rate for those who did not develop CIAKI was 3.3%, which was significantly lower than the 9.4% mortality rate for those who did develop CIAKI.\textsuperscript{20} Although reports link CIAKI onset and vital prognosis, it is currently not known if the complication of CIAKI is a predictor for poor vital prognosis, or if having a poor general prognosis is a predictor for CIAKI onset.

### Differential Diagnosis

The most important disease from which CIAKI must be differentiated is cholesterol embolism. Cholesterol embolism is a disorder that results in renal dysfunction and generally has a poor prognosis. It can be caused by intravascular catheter placement or anticoagulant therapy, both of which can cause cholesterol crystal formation when atheromatous plaques in the aorta break free and occlude renal arteries, arterioles, and glomerular capillaries, particularly those with a diameter of 100–300 μm. Cholesterol embolism is characterized by progressively decreasing renal function that may be delayed several days or weeks after a catheter procedure.\textsuperscript{21,22} The following list gives the main points of differentiation between cholesterol embolism and CIAKI. Cholesterol embolism is characterized by the following:

1. A delay of several days or weeks after a catheter procedure and then a progressive decrease in renal function.
2. The renal dysfunction is generally irreversible, and in many cases follows a progressive course.
3. In addition to renal dysfunction, embolism causes multiple organ disorders.
4. Symptoms of systemic embolism include livedo reticu-

### Table 2 Risk scores for CIAKI

| Risk factor                        | Score |
|------------------------------------|-------|
| Hypotension                        | 5     |
| Intra-aortic balloon pump          | 5     |
| Congestive heart failure           | 5     |
| Age > 75 years                     | 4     |
| Anemia                             | 3     |
| Diabetes                           | 3     |
| Contrast medium dose               | 1 per 100 mL |
| Serum creatinine level > 1.5 mg/dl | 4     |
| Or                                 |
| eGFR                               |
| 2: eGFR 40–60                      |
| 4: eGFR 20–< 40                    |
| 6: eGFR < 20                       |

### Table 3 Association of risk score and risk of CIAKI and dialysis

| Total risk score | CIAKI risk | Dialysis risk |
|------------------|------------|---------------|
| 0–5              | 7.5%       | 0.04%         |
| 6–10             | 14.0%      | 0.12%         |
| 11–16            | 26.1%      | 1.09%         |
| > 16             | 57.3%      | 12.6%         |
laris in the lower limbs, cyanosis, blue toes, and other dermatological symptoms.
5. Vasculitis-like findings such as fever, joint pain, generalized malaise, eosinophilia, elevated C-reactive protein, decreased serum complement, and elevated sedimentation rate.
6. As part of a definitive diagnosis, pathological diagnosis via skin and kidney biopsy is required.

Biomarkers

Serum creatinine is suggested as a biomarker in the Japanese CIAKI guidelines, but its sensitivity is low in cases of early decreases in GFR. Because serum creatinine does not increase until the GFR decreases to approximately 40 mL/min/1.73 m², there is a danger that renal function will be overestimated. Serum creatinine may also be underestimated in cases of anemia and hypervolemia. Currently, there is no alternative to the use of serum creatinine, which is easy to measure, but new biomarkers for renal function monitoring are required to avoid the limitations of serum creatinine. Although a variety of biomarkers have been investigated and reported, there has been no major advance in this area.

Because serum cystatin C increases even when renal dysfunction has reduced GFR to only approximately 70 mL/min/1.73 m², it is an effective marker for early diagnosis. Its further merits include the fact that it is not affected by muscle mass, diet, or exercise. However, much about serum cystatin C remains to be elucidated, and some reports have indicated that serum cystatin C levels are affected by pregnancy, HIV infection, thyroid dysfunction, and drugs. Consequently, further study is required.

A recent report on the Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury trial, a multicenter prospective study investigating neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) levels in serum and urine, indicated that NGAL and IL-18 are useful as biomarkers of AKI. In addition, recent reports on the usefulness of urinary levels of insulin-like growth factor-binding protein-7 and tissue inhibitor of metalloproteinase-2 as biomarkers of AKI have gained attention. More of these types of studies on biomarkers are required to identify biomarkers that can be used in the clinical setting.

Prevention

When performing procedures utilizing contrast medium on patients with risk factors for CIAKI, it is necessary to implement appropriate preventive measures. Currently, the most commonly recommended preventative measure is transfusion before and after the contrast medium procedure. The specific protocol calls for replacement of physiological saline solution at the rate of 1 mL/kg/h for 12 h before and after the procedure. This protects the blood flow to the renal parenchyma by increasing extracellular fluid and is thought to suppress the onset of CIAKI by reducing the concentration of contrast medium within the renal tubule lumen. Careful interpretation is necessary, however, because this protocol is not the established optimum protocol, but rather is the standard transfusion method used as the control in many clinical studies.

When there is insufficient time for the above transfusion protocol before the start of a contrast medium procedure, a protocol calling for isotonicity-adjusted sodium bicarbonate solution (152 mEq/L) to be administered at 3 mL/kg/h for 1 h prior to contrast medium administration and at 1 mL/kg/h for 6 h following the procedure is considered to help prevent CIAKI. The mechanism for this is thought to involve increased blood flow to the renal parenchyma, which then suppresses the production of tubular epithelial cell free radicals by bicarbonate. However, the use of short-term transfusions is not recommended because it may increase the risk of CIAKI, in contrast to the effects of long-term transfusions. There is insufficient evidence to support the idea that simply drinking water can suppress the onset of CIAKI in the same way as a transfusion. Currently, it is recommended that patients receive transfusions rather than simply drink water as a form of fluid replacement. In addition, most studies report that blood purification therapy...
is not effective in preventing CIAKI.\textsuperscript{37–40} Pharmacotherapies previously thought to have the potential to prevent CIAKI include N-acetylcysteine, (hANP), ascorbic acid, and statin, but the effectiveness of these drugs has since been ruled out. In a meta-analysis of 26 randomized controlled trials on the effects of N-acetylcysteine, it was found that N-acetylcysteine had a prophylactic effect at a relative risk of 0.62.\textsuperscript{41} However, questions have been raised regarding the validity of these conclusions.\textsuperscript{42}

### Treatment

The most effective ways to prevent CIAKI, as with AKI from other causes, are the above-mentioned preventative measures. Additionally, although it is not effective as a preventative measure, early emergency blood purification therapy for CIAKI patients in poor general condition and with accompanying oliguria may improve either mortality rate or renal function and is recommended for this reason.\textsuperscript{43,44}

However, while the effects of diuretics,\textsuperscript{45,46} hANP,\textsuperscript{47,48} and low-dose dopamine,\textsuperscript{49,50} among others, are currently being investigated, no clearly effective drug has currently been identified. Additionally, the effectiveness of transfusion therapy after CIAKI onset has not yet been elucidated, and, because the risk of mortality may be increased by increasing the volume of body fluid, transfusion therapy that increases body fluid volume over the appropriate stasis level is not recommended.\textsuperscript{51,52}

### Future Directions

As mentioned above, the only recommendation for the prevention of CIAKI is long-term transfusion prior to contrast medium administration. However, this is not practical in emergency situations. Thus, we recently created contrast medium model rats and reported on our investigation of the effectiveness of hydrogen gas inhalation as a preventative for CIAKI.\textsuperscript{53} Specifically, we investigated the effect on renal function and renal tissue of hydrogen gas inhalation by rats on administration of contrast medium, as compared to rats who inhaled a control gas. The results indicated that the inhalation of hydrogen gas suppressed the decrease in renal function caused by the administration of contrast medium. Immunostaining using 8-hydroxy-2’-deoxyguanosine (8-OHdG), a marker for oxidative stress, indicated that there were significantly fewer 8-OHdG-positive cells in renal tissue in the hydrogen gas group. We therefore believe that the suppression of oxidative stress by hydrogen gas inhalation is one mechanism for the suppression of renal dysfunction. Because the administration of hydrogen gas takes place only when the contrast medium is administered, there is no need for time-consuming procedures before contrast medium administration. This fact may make it effective for use on emergency patients who cannot be provided with sufficient fluid replacement before emergency contrast medium administration. Preparations are underway for a clinical study to address this issue.

### Conclusion

For patients at risk of developing CIAKI, the advisability of the use of a contrast agent needs to be carefully taken into consideration. If alternative tests such as magnetic resonance imaging are available, the latter should be carried out instead. However, in clinical settings, the potential benefits of the use of contrast agents often exceed the risk of developing CIAKI. Consequently, the decision to use a contrast agent should primarily be made by consideration of the patient’s ultimate benefit, and tests using contrast agents should still be performed if necessary. In such cases, preventive measures against CIAKI are of the utmost importance and must be implemented; establishment of a therapeutic framework for use in cases of CIAKI is also crucial. Ultimately, the development of new preventive measures, such as hydrogen gas inhalation, is needed to deal with emergent cases in which it is impossible to provide sufficient fluid replacement before the administration of contrast medium.

### References

1. 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. [Medline] [CrossRef]
2. http://www.esur.org/Contrast-media.51.0.html.
3. Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S: Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int 1991; 40: 632–642. [Medline] [CrossRef]
4. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC: Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol 1990; 258: F115–F120. [Medline]
5. Itoh Y, Yano T, Sendo T, Sueyasu M, Hirano K, Kanaide H, Oishi R: Involvement of de novo ceramide synthesis in radiocontrast-induced renal tubular cell injury. Kidney Int 2006; 69: 288–297. [Medline] [CrossRef]
6. Schick CS, Haller C: Comparative cytotoxicity of ionic and non-ionic radiocontrast agents on MDCK cell monolayers in vitro. Nephrol Dial Transplant 1999; 14: 342–347. [Medline] [CrossRef]
7. Peer A, Averbukh Z, Berman S, Modai D, Averbukh M, Weissgarten J: Contrast media augmented apoptosis of cultured renal mesangial, tubular, epithelial, endothelial, and hepatic cells. Invest Radiol 2003; 38: 177–182. [Medline] [CrossRef]
8. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J, CIN Consensus Working Panel: Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 2006; 98: 5K–13K.
9. Nyman U, Björk J, Aspelin P, Marenzi G: Contrast medium dose-to-GFR ratio: a measure of systemic exposure to predict contrast-induced nephropathy after percutaneous coronary intervention. Acta Radiol 2008; 49: 658–667. [Medline] [CrossRef]
10. McCullough PA: Contrast-induced acute kidney injury. J Am Coll Cardiol 2008; 51: 1419–1428. [Medline] [CrossRef]

11. 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; 86: 649–652. [Medline] [CrossRef]

12. Lufti V, Hoogestraat-Lufti I, Fels LM, Egbeoyung-Baiyee D, Tusch G, Galanski M, Olbricht CJ: Contrast media nephropathy: intravenous CT angiography versus intraarterial digital subtraction angiography in renal artery stenosis: a prospective randomized trial. Am J Kidney Dis 2002; 40: 236–242. [Medline] [CrossRef]

13. Mehran R, Faxon D, Quinlan DJ, Ewy GA, Mintz GS, 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 intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 2013; 267: 119–128. [Medline] [CrossRef]

14. Kim SM, Cha RH, Lee JP, Kim DK, Oh KH, Joo KW, Lim CS, Kim S, Kim YS: Incidence and outcomes of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393–1399. [Medline]

15. Mitchell AM, Jones AE, Tumlin JA, Kline JA: Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. Clin J Am Soc Nephrol 2010; 5: 4–9. [Medline]

16. Homma K, Yoshida T, Yoshizawa J, Suzuki M, Sasaki J, Namiki J, Hayashi M, Horii S: Preventing contrast-induced acute kidney injury in the emergency room. Acute Med Surg 2016; 3: 59–60.

17. 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. [Medline] [CrossRef]

18. Goldenberg I, Chonchol M, Guetta V: Reversible acute kidney injury following contrast exposure and the risk of long-term mortality. Am J Nephrol 2009; 29: 136–144. [Medline] [CrossRef]

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 intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 2013; 267: 119–128. [Medline] [CrossRef]

20. Senoo T, Motohiro M, Kamihata H, Yamamoto S, Isono T, Ma-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 intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 2013; 267: 119–128. [Medline] [CrossRef]

21. Modi KS, Rao VK: Atheroembolic renal disease. J Am Soc Nephrol 2001; 12: 1781–1787. [Medline]

22. Scolari F, Tardanico R, Zani R, Pola A, Viola BF, Movilli E, Maiorca R: Cholesterol crystal embolism: A recognizable cause of renal disease. Am J Kidney Dis 2000; 36: 1089–1109. [Medline] [CrossRef]

23. Doi K, Yuen PS, Eisner C, Hu X, Leelahavanichkul A, Schenmann J, Star RA: Reduced production of creatinine limits its use as a marker of kidney injury in sepsis. J Am Soc Nephrol 2009; 20: 1217–1221. [Medline] [CrossRef]

24. Liu KD, Thompson BT, Ancukiewicz M, Steinrubg JS, Douglas IS, Matthay MA, Wright P, Peterson MW, Rock P, Hyzy RC, Anzueto A, Truwit JD, National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network: Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med 2011; 39: 2665–2671. [Medline] [CrossRef]

25. Pucci L, Triscornia S, Lucchesi D, Fotino C, Pellegrini G, Pardini A, Vescarelli E, Miccoli R, Del Prato S, Penno G: Cystatin C and estimates of renal function: searching for a better measure of kidney function in diabetic patients. Clin Chem 2007; 53: 480–488. [Medline] [CrossRef]

26. Tanaka A, Suemaru K, Araki H: A new approach for evaluating renal function and its practical application. J Pharmacol Sci 2007; 105: 1–5. [Medline] [CrossRef]

27. Jayagopal V, Kecivel BG, Atkin SL, Jennings PE, Kilpatrick ES: Paradoxical changes in cystatin C and serum creatinine in patients with hypo- and hyperthyroidism. Clin Chem 2003; 49: 680–681. [Medline] [CrossRef]

28. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelestein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX, TRIBE-AKI Consortium: Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011; 22: 1748–1757. [Medline] [CrossRef]

29. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cey CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnesson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullane S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17: R25. [Medline] [CrossRef]

30. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, Fitzgerald R, Gong MN, Graham DD, Gunnesson K, Heung M, Jortani S, Kleerup E, Koyner JL, Krell L, Letourneau J, Lissauer M, Miner J, Nguyen HB, Ortega LM, Self WH, Sellman R, Shi J, Tracesecky S, Zalados JE, Wilber ST, Walker MG, Wilson J, Wunderink R, Zimmerman J, Kellum JA: Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014; 189: 932–939. [Medline] [CrossRef]

31. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J: A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 2003; 93: c29–c34. [Medline] [CrossRef]

32. Lee SW, Kim WJ, Kim YH, Park SW, Park DW, Yun SC, Lee JY, Kang SJ, Lee CW, Lee JH, Choi SW, Sehgal AR: Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: the OTHER CAN study. J Invasive Cardiol 2003; 15: 1393–1399. [Medline] [CrossRef]

33. Zoungas S, Ninomiya T, Huxley R, Cass A, Jardine M, Gallagher M, Patel A, Vasheghani-Farahani A, Sadigh G, Perkovic V: Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med 2009; 151: 631–638. [Medline] [CrossRef]

34. Navaneethan SD, Singh S, Appasamy S, Wing RE, Sehgal AR: Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Kidney Dis 2011; 57: 1447–1452. [Medline] [CrossRef]

35. Zoungas S, Ninomiya T, Huxley R, Cass A, Jardine M, Gallagher M, Patel A, Vasheghani-Farahani A, Sadigh G, Perkovic V: Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med 2009; 151: 631–638. [Medline] [CrossRef]

36. Krasuski RA, Beard BM, Geoghagan JD, Thompson CM, Guidera SA: Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. J Invasive Cardiol 2003; 15: 699–702. [Medline] [CrossRef]

37. Vogt B, Ferrari P, Schönhölzer C, Marti MH, Mohaupt M, Wiederkehr M, Cereghetti C, Serra A, Huynh-Do U, Uehlinger D,
Frey FJ: Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am J Med 2001; 111: 692–698. [Medline] [CrossRef]

38. Sterner G, Frennby B, Kurkus J, Nyman U: Does post-angiographic hemodialysis reduce the risk of contrast-medium nephropathy? Scand J Urol Nephrol 2000; 34: 323–326. [Medline] [CrossRef]

39. Lehnert T, Keller E, Gondolf K, Schäffner T, Pavenstädt H, Schollmeyer P: Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant 1998; 13: 358–362. [Medline] [CrossRef]

40. Frank H, Werner D, Lorusso V, Klinghammer L, Daniel WG, Kunzendorf U, Ludwig J: Simultaneous hemodialysis after contrast medium administration during coronary angiography fails to prevent radiocontrast-induced nephropathy in chronic renal failure. Clin Nephrol 2003; 60: 176–182. [Medline] [CrossRef]

41. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC: Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008; 148: 284–294. [Medline] [CrossRef]

42. Trivedi H: Is there enough evidence to support use of N-acetylcysteine in contrast-induced nephropathy? Ann Intern Med 2008; 149: 213, author reply 215–216. [Medline] [CrossRef]

43. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL: Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis 2008; 52: 272–284. [Medline] [CrossRef]

44. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Maceo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA: Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 2009; 24: 129–140. [Medline] [CrossRef]

45. Hager B, Betschart M, Krapf R: Effect of postoperative intravenous loop diuretics on renal function after major surgery. Schweiz Med Wochenschr 1996; 126: 666–673. [Medline]

46. Shilliday IR, Quinn KJ, Allison ME: Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. Nephrol Dial Transplant 1997; 12: 2592–2596. [Medline] [CrossRef]

47. Allgren RL, Marbury TC, Rahman SN, Weisberg LS, Fenves AZ, Lafayette RA, Sweet RM, Genter FC, Kurnik BR, Conger JD, Sayegh MH, Auriculine Anaritide Acute Renal Failure Study Group: Anaritide in acute tubular necrosis. N Engl J Med 1997; 336: 828–834. [Medline] [CrossRef]

48. Lewis J, Salem MM, Chertow GM, Weisberg LS, McGrew F, Marbury TC, Allgren RL, Anaritide Acute Renal Failure Study Group: Atrial natriuretic factor in oliguric acute renal failure. Am J Kidney Dis 2000; 36: 767–774. [Medline] [CrossRef]

49. Abizaid AS, Clark CE, Mintz GS, Dosa S, Popma JJ, Pichard AD, Satler LF, Harvey M, Kent KM, Leon MB: Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999; 83: 260–263, A5. [Medline] [CrossRef]

50. Australian and New Zealand Intensive Care Society(ANZICS) Clinical Trials Group: Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Lancet 2000; 356: 2139–2143. [Medline] [CrossRef]

51. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL, Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008; 12: R74. [Medline] [CrossRef]

52. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL, Program to Improve Care in Acute Renal Disease (PICARD) Study Group: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009; 76: 422–427. [Medline] [CrossRef]

53. Homma K, Yoshida T, Yamashita M, Hayashi M, Hori S: Inhalation of hydrogen gas is beneficial for preventing contrast-induced acute kidney injury in rats. Nephron, Exp Nephrol 2014; 128: 116–122. [Medline] [CrossRef]