REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Contrast-Associated Acute Kidney Injury

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Contrast-associated acute kidney injury is characterized by a decrease in kidney function that occurs within days after the intravascular administration of iodinated contrast material. In the 1950s, initial cases were reported in patients with preexisting kidney disease who were undergoing intravenous pyelography with contrast agents that were associated with a high incidence of acute kidney injury and other adverse effects.[1-4] Over time, an evolution in the design of contrast agents, improved recognition of risk factors, and implementation of preventive care resulted in lower rates of acute kidney injury after the administration of contrast material[5-7] (Fig. 1). More recent studies have suggested that the risk of acute kidney injury due to contrast material is overestimated.[9-13] Such studies are important, considering that angiographic procedures may be underused in patients with chronic kidney disease who present with conditions such as acute coronary syndromes, presumably because of concern about precipitating acute kidney injury.[14] This review summarizes the pathophysiology of contrast-associated acute kidney injury, the diagnostic criteria, and risk stratification; discusses current controversies regarding the incidence of this condition; and highlights studies that have provided the evidence that forms the basis for preventive care.

Pathophysiology, Definition, and Risk Estimation

Although the pathophysiological mechanisms by which contrast agents cause kidney injury have not been completely elucidated, direct and indirect effects, as well as hemodynamic perturbations, have been implicated[15,16] (Fig. 2). Contrast agents are directly toxic to tubular epithelial cells, leading to loss of function and both apoptosis and necrosis. Indirect mechanisms are related to ischemic injury due to vasomotor changes mediated by vasoactive substances such as endothelin, nitric oxide, and prostaglandins. The outer renal medulla has a relatively low partial pressure of oxygen, which when coupled with enhanced metabolic demand, makes the medulla particularly susceptible to the hemodynamic effects of contrast material.[17]

Historically, the decline in kidney function after the intravascular administration of iodinated contrast material was referred to as contrast-induced nephropathy and commonly defined as an increase in the plasma creatinine level of at least 0.5 mg per deciliter (44 μmol per liter) or at least a 25% increase from the baseline level within 2 to 5 days after exposure to contrast material.[18-21] The Kidney Disease Improving Global Outcomes (KDIGO) working group proposed the term "contrast-induced acute kidney injury" and suggested a definition based on a plasma creatinine level that has increased by a factor of 1.5 times or more over the baseline value within 7 days after exposure to contrast medium, a plasma creatinine level

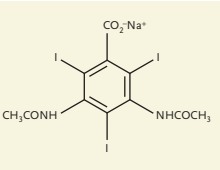
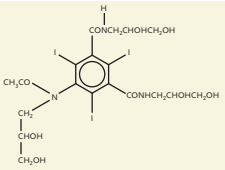
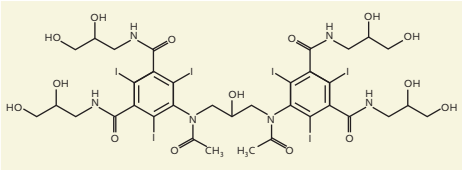
	High Osmolality	Low Osmolality		Iso-osmolality
Molecular Structure				
	Ionic monomer	Ionic dimer	Nonionic monomer	Nonionic dimer
Generic Name (mg contrast/ml)	Diatrizoate meglumine and diatrizoate sodium (760)	Ioxaglate meglumine and ioxaglate sodium (589)	Iopamidol (408) Iopamidol (510) Iopamidol (612) Iopamidol (755)	Iodixanol (550) Iodixanol (652)
Iodine Concentration (mg/ml)	370	320	200–370	270–320
Osmolality (mOsm/kg H_2O)	1551	~600	413–796	290
Viscosity (mPa·sec at 37°C)	10.5	7.5	2.0–9.4	6.3–11.8

Figure 1. Classification of Available Contrast Agents.

Contrast agents are classified according to osmolality. Examples of molecular structures and specific agents are shown, and characteristics are described according to the American College of Radiology's *Manual on Contrast Media*.[8]

that has increased by at least 0.3 mg per deciliter (26.5 μmol per liter) over the baseline value within 48 hours after exposure to contrast medium, or a urinary volume of less than 0.5 ml per kilogram of body weight per hour that persists for at least 6 hours after exposure.[22] Although the plasma creatinine component of this definition has reasonable sensitivity, its specificity is poor, because plasma creatinine levels fluctuate owing to fluid shifts and medication effects. Since other factors (e.g., medications, hypotension, or atheroemboli) can precipitate acute kidney injury after exposure to contrast medium, the term "contrast-associated acute kidney injury" has gained favor.

The risk of acute kidney injury after the administration of contrast material is also influenced by patient- and procedure-related factors. Preexisting chronic kidney disease is the strongest patient-related risk factor, with lower levels of kidney function associated with higher degrees of risk.[23] An analysis of data from 985,737 patients undergoing percutaneous coronary intervention (PCI) confirmed that severe chronic kidney disease was the strongest independent risk factor for contrast-associated acute kidney injury.[24] Although diabetes mellitus is commonly cited as a risk factor, data from the Iohexol Cooperative Study, performed more than 20 years ago, showed that it was not an independent risk factor but rather amplified susceptibility in patients with underlying chronic kidney disease.[25] As compared with the early, high-osmolality contrast agents, low-osmolality and iso-osmolality agents are associated with a lower risk of kidney injury and their use is recommended (class I recommendation, level of evidence A) by the European Society of Cardiology and the American Heart Association–American College of Cardiology.[25-28] Use of contrast medium at a high volume (>350 ml or >4 ml per kilogram) or repeated administration within 72 hours after initial administration has been shown to be associated with an increased risk.[18,29]

There is also evidence that the risk of acute kidney injury varies with the clinical presentation and the type of imaging procedure. For example, patients with ST-segment elevation myocardial infarction who undergo PCI have a particularly high risk of contrast-associated kidney injury.[30]

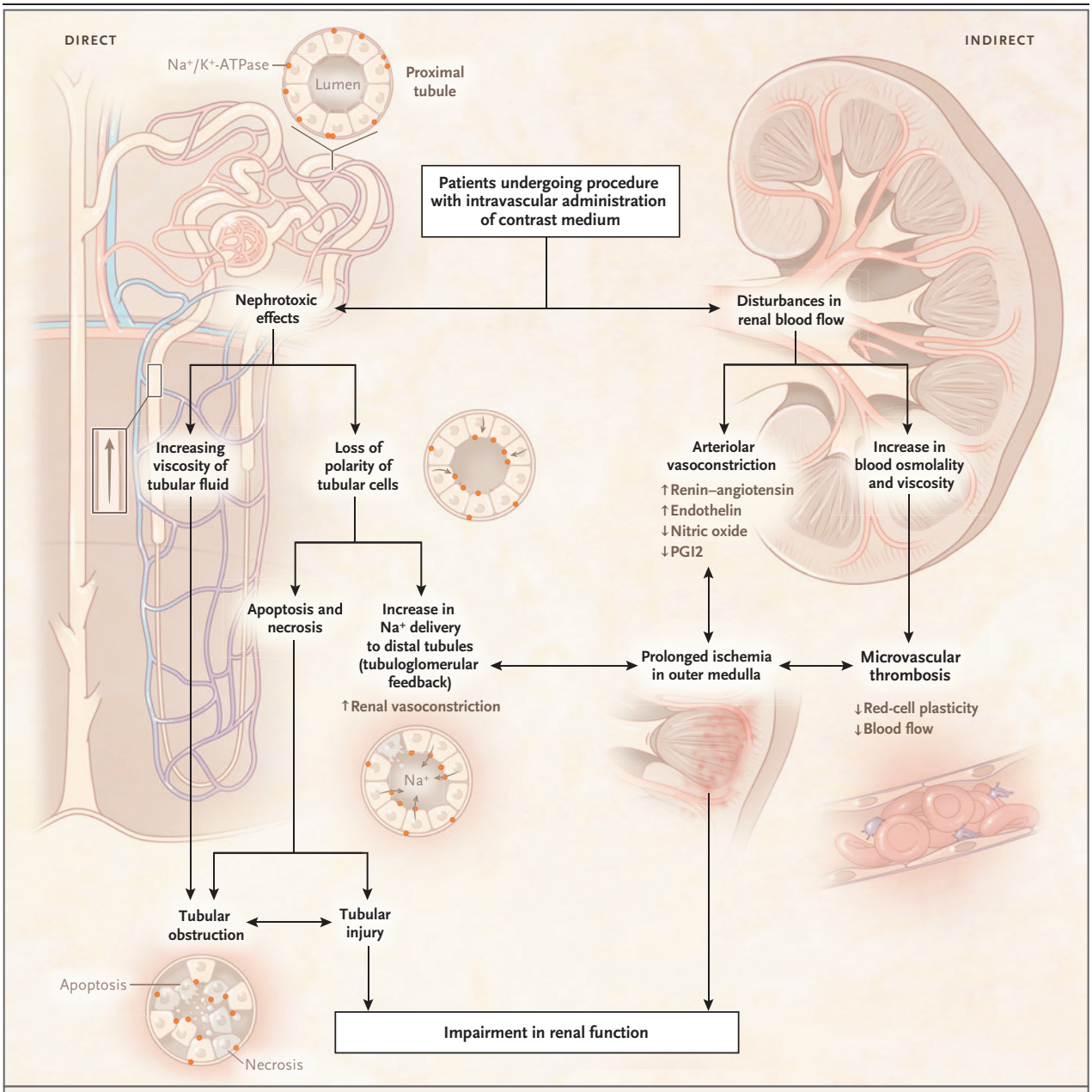


Figure 2. Proposed Mechanisms of Contrast-Associated Acute Kidney Injury.

Direct mechanisms of kidney injury from exposure to contrast agents are thought to be due to nephrotoxic effects on the tubular epithelium, leading to loss of function, apoptosis, and eventually, necrosis. Such effects are related to the biochemical properties of the particular contrast medium. At the level of the individual nephron, early tubular epithelial injury is characterized by the loss of cell polarity due to the redistribution of Na^+/K^+-ATPase from the basolateral to the luminal surface of the tubular cells, resulting in abnormal ion transport across the cells and increased sodium delivery to the distal tubules. This phenomenon leads to further renal vasoconstriction through tubuloglomerular feedback. With the progression of cellular injury, epithelial cells detach from the basement membranes and cause luminal obstruction, increased intratubular pressure, and finally, a decrease in the glomerular filtration rate. Indirect effects of contrast agents involve ischemic injury from regionally or globally decreased perfusion. Contrast agents may lead to intrarenal vasoconstriction locally mediated by vasoactive substances such as endothelin, nitric oxide, and prostaglandin, resulting in reduced glomerular blood flow and reduced oxygen delivery to the metabolically active parts of the nephron. In addition, contrast agents increase blood viscosity, leading to further reduction of the microcirculatory flow and to changes in blood osmolality, which in turn impair the plasticity of erythrocytes and may increase the risk of microvascular thrombosis.

It is generally believed that arteriography is associated with a higher risk than computed tomography (CT), owing to delivery of more concentrated contrast material to the kidneys with arteriographic procedures and the higher overall risk profile of patients requiring such procedures.

A series of risk-stratification models that incorporate patient and procedural factors have been validated in past studies (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[18,31-34] A strength of these risk-stratification models is that they are derived from data based on large numbers of patients. However, there are caveats to their clinical use — namely, the inclusion of variables (e.g., the volume of contrast material administered and use or nonuse of a hemodynamic-support device) that are unknown before the procedure. Furthermore, most of these models were developed in studies involving patients undergoing PCI, which limits their generalizability.

SERIOUS ADVERSE OUTCOMES AND IMPLICATIONS FOR CLINICAL PRACTICE

Many studies have shown that contrast-associated acute kidney injury, defined by small decrements in kidney function, is associated with increased mortality.[31,35-41] Contrast-associated acute kidney injury is also correlated with accelerated progression of underlying chronic kidney disease. James et al. reported that the risk of a sustained reduction in kidney function at 90 days was greater for patients who had acute kidney injury after undergoing coronary angiography than for those who did not have acute kidney injury.[42] For patients with mild acute kidney injury, the adjusted odds ratio was 4.7 (95% confidence interval [CI], 3.9 to 5.7), and for those with more severe acute kidney injury, the adjusted odds ratio was 17.3 (95% CI, 12.0 to 24.9), supporting a graded relationship between the severity of acute kidney injury and the risk of sustained kidney impairment. Accordingly, deteriorating kidney function after angiography or angioplasty has been characterized as a major procedural complication in the National Cardiovascular Data Registry.[24]

Collectively, these studies and others with similar findings undoubtedly raised awareness of contrast-associated acute kidney injury and spurred research to identify preventive strategies. However, the reports are solely associational (Fig. S1 in the Supplementary Appendix). It is plausible that contrast-associated acute kidney injury is a marker of an increased risk of serious adverse outcomes rather than a mediator of such outcomes. Support for such a view derives from a study by Lassnigg et al.,[43] who found that although small postsurgical elevations in plasma creatinine levels were associated with increased 30-day mortality, small decrements in plasma creatinine levels (≤0.5 mg per deciliter) were also associated with increased mortality (hazard ratio, 2.27; 95% CI, 1.28 to 4.03). Such fluctuations (up or down) in plasma creatinine levels after surgical or radiographic procedures are probably due to hemodynamic instability, decreased renovascular autoregulation, or both, rather than an actual cause of adverse downstream events. A meta-analysis by Coca et al. showed that interventions that reduced the incidence of acute kidney injury by nearly 50% failed to reduce the risk of longer-term death (relative risk, 0.97; 95% CI, 0.82 to 1.16) or the development of chronic kidney disease (relative risk, 0.87; 95% CI, 0.52 to 1.46).[44] These observations raise doubt about causation between small increments in plasma creatinine levels after the administration of contrast material and adverse downstream events; they also underscore the problem in defining contrast-associated acute kidney injury on the basis of small increments in a biologic marker (i.e., plasma creatinine) that are neither specific for injury due to the administration of contrast material nor definitively indicative of intrinsic kidney damage. To date, there have been no adequately powered clinical trials showing that prevention of contrast-associated acute kidney injury results in a survival benefit.

Whether contrast-associated acute kidney injury represents a mediator or a marker of adverse outcomes, it appears likely that the many studies documenting these associations have had important unintended consequences for clinical care. A large and growing number of studies have shown that patients with chronic kidney disease are less likely to undergo coronary angiography and revascularization than patients who do not have chronic kidney disease.[14,45-57] It has been hypothesized that concern about the risk of contrast-associated acute kidney injury explains these

findings. This is of considerable importance, given current uncertainty about the causal relationship between contrast-associated acute kidney injury and serious adverse outcomes, the substantial morbidity and mortality related to cardiovascular disease among patients with chronic kidney disease, and clinical practice guidelines that support the use of invasive care (e.g., angiography) for the management of acute coronary syndromes in most patients with moderate kidney impairment. Studies showing differences in the use of angiography based on the presence or absence of chronic kidney disease underscore the urgent need to determine the true risk of clinically significant acute kidney injury in the large and growing population of patients undergoing contrast-enhanced procedures.

NEPHROTOXICITY OF CONTRAST MATERIAL IN CURRENT PRACTICE

Over the past decade, multiple studies have compared the risk of acute kidney injury after procedures performed with and those performed without intravascular administration of contrast material. A meta-analysis by McDonald et al. that involved 25,950 patients showed no significant difference in the risk of acute kidney injury between patients who underwent procedures with intravenous administration of iodinated contrast material and those who underwent procedures without it (6.4% and 6.5%, respectively; risk ratio, 0.79; 95% CI, 0.62 to 1.02; P=0.07).[58] The incidence rates of dialysis and death were also similar in the two groups. Another meta-analysis showed a lower risk of acute kidney injury among patients with acute ischemic stroke who underwent CT with intravenous administration of contrast material, as compared with patients who underwent CT without the use of contrast material (odds ratio, 0.47; 95% CI, 0.33 to 0.68; P<0.01).[59] Other studies have reported similar findings.[60,61]

Residual confounding and indication bias are major limitations of such studies. Despite the use of propensity-score matching in some studies, higher-risk patients are less likely to be exposed to contrast material than are lower-risk patients. This likelihood is underscored by the finding in several studies of lower rates of acute kidney injury among patients who were exposed to contrast material than among those who were not, an observation that should not be construed as indicating a nephroprotective effect of contrast material.[59,61] These analyses uniformly concluded that intravascular administration of iodinated contrast material does not appear to be associated with an increased risk of acute kidney injury.

Research reveals that the nominal increments in plasma creatinine levels that are used to define acute kidney injury are not uncommon in patients who have undergone contrast-enhanced procedures, nor are such increases uncommon among hospitalized patients in general.[60,62] However, the incidence of severe acute kidney injury due to contrast material is quite low. A study that prospectively assessed the development of contrast-associated acute kidney injury among patients with chronic kidney disease who were undergoing nonemergency coronary angiography showed that 1.2% of the patients had a postprocedure increase in the plasma creatinine level that was 50% or more of the baseline value, and none had an increase of 100% or more or required dialysis.[7] In a meta-analysis of studies involving patients who underwent contrast-enhanced CT, the rate of post-procedure dialysis was just 0.3%.[58] Hence, although currently available data are insufficient to declare that contrast agents are not nephrotoxic, severe acute kidney injury characterized by substantial decrements in kidney function, the need for renal replacement therapy, or both appears to be very infrequent after intravascular contrast administration. Accordingly, a prudent approach to the care of patients undergoing contrast-enhanced procedures involves judicious implementation of evidence-based preventive care for patients identified as being at highest risk for acute kidney injury.

PREVENTIVE STRATEGIES

Research on the prevention of contrast-associated acute kidney injury has focused principally on the use of renal replacement therapies, pharmaceutical agents, and intravenous crystalloid. The benefits of prophylactic renal replacement therapy and of most pharmaceutical agents have not been proved, rendering the provision of periprocedural intravenous crystalloid the primary intervention to mitigate risk. Here we summarize data from studies investigating the use of intravenous fluids and certain pharmaceutical agents to prevent contrast-associated acute kidney injury.

INTRAVASCULAR VOLUME EXPANSION

Although several observational studies have shown a protective effect of intravenous fluids, evidence from randomized clinical trials is relatively sparse. A study by Trivedi et al. that randomly assigned patients undergoing angiography to receive intravenous isotonic saline or unrestricted oral fluids was stopped after 53 patients were enrolled, owing to a markedly lower incidence of contrast-related acute kidney injury with saline (3.7% vs. 34.6%, P=0.005).[63] Mueller et al. reported a lower rate of contrast-associated acute kidney injury with periprocedural use of isotonic saline as compared with periprocedural use of half-isotonic saline (0.7% vs. 2.0%, P=0.04).[64] However, the patients in this study had a low baseline risk. Current American College of Radiology guidelines on the administration of contrast material recommend the use of intravenous isotonic saline at an infusion rate of 100 ml per hour for 6 to 12 hours before and 4 to 12 hours after angiography.[8] European Society of Cardiology guidelines on myocardial revascularization recommend intravenous isotonic saline at a rate of 1 to 1.5 ml per kilogram per hour for 12 hours before and up to 24 hours after the procedure.[28] A shorter protocol that is more practical for outpatients and those undergoing urgent procedures comprises an intravenous infusion of isotonic saline for 1 to 3 hours before and 6 hours after the procedure.[65]

Despite such recommendations, a recent noninferiority trial challenged the tenet that intravenous fluids are effective. In the AMACING (A Maastricht Contrast-Induced Nephropathy Guideline) trial, which randomly assigned 660 patients undergoing contrast-enhanced procedures to receive either periprocedural intravenous isotonic saline or no intravenous fluids, there was no significant difference in the incidence of acute kidney injury between the hydration group and the no-hydration group (2.7% and 2.6%, respectively; absolute difference, −0.1 percentage point; 95% CI, −2.25 to 2.06).[21] However, the validity of this finding is diminished by substantial underenrollment (although the initial plan was to enroll 1300 patients, only 660 patients underwent randomization), low rates of intraarterial procedures (48%) and interventional procedures (16%), and moderate chronic kidney disease in a majority of patients. Consequently, it is premature to conclude that intravenous fluids are ineffective or unnecessary on the basis of the results of this trial.

The volume of intravenous fluid necessary for the prevention of acute kidney injury in patients undergoing contrast-enhanced imaging procedures, including those with underlying heart failure, is unknown. The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial compared standard intravenous administration of fluid with a strategy of fluid administration based on measured left ventricular end-diastolic pressure.[20] All patients received 0.9% isotonic saline at a rate of 3 ml per kilogram per hour for 1 hour before undergoing coronary angiography. The control group continued to receive isotonic saline at a rate of 1.5 ml per kilogram per hour during the procedure and for 4 hours afterward, whereas the pressure-guided group received isotonic saline at a rate of 5 ml per kilogram per hour, 3 ml per kilogram per hour, or 1.5 ml per kilogram per hour for left ventricular end-diastolic pressure of less than 13 mm Hg, 13 to 18 mm Hg, and more than 18 mm Hg, respectively. The incidence of acute kidney injury was lower in the pressure-guided group than in the control group (6.7% vs. 16.3%; relative risk, 0.41; 95% CI, 0.22 to 0.79; P=0.005), with a very low overall rate of pulmonary compromise.[20] Similar results were reported by Qian and colleagues, who used right atrial pressure to guide intravascular volume expansion.[66] Although volume expansion was associated with an acceptable side-effect profile in these studies, including among patients with clinically significant elevations in filling pressures at baseline, the intravenous fluid and sodium loads may need to be reduced in cases of heart failure or severe hypertension.

Multiple trials, many with small samples, along with subsequent meta-analyses, have compared intravenous isotonic sodium bicarbonate with isotonic sodium chloride for the prevention of contrast-associated acute kidney injury, on the hypothesis that urinary alkalinization would reduce contrast-induced generation of injurious oxygen free radicals. The highly divergent results of these trials and resultant clinical equipoise formed the basis for the Prevention of Serious Adverse Events Following Angiography (PRESERVE) study.[19] In a 2-by-2 factorial design, this double-blind trial randomly assigned 5177 high-risk patients undergoing nonemergency angiography

to receive intravenous isotonic sodium bicarbonate or intravenous isotonic saline, as well as oral acetylcysteine or oral placebo, for the prevention of a primary 90-day composite end point comprising death, need for dialysis, or persistent impairment in kidney function. The trial, which was stopped early because of futility, showed no significant difference in the incidence of the primary outcome (4.4% with bicarbonate and 4.7% with saline; odds ratio, 0.93; 95% CI, 0.72 to 1.22; P=0.62) or in the incidence of contrast-associated acute kidney injury, which was a secondary end point (9.5% with bicarbonate and 8.3% with saline; odds ratio, 1.16; 95% CI, 0.96 to 1.41; P=0.13). Although the exclusion of patients undergoing emergency procedures and a low overall median volume of contrast material administered (85 ml) were limitations of this trial, its large size, robust statistical power, and use of a clinically relevant primary end point were important strengths affirming the investigators' conclusion that isotonic sodium bicarbonate provides no benefit relative to isotonic saline.

ACETYLCYSTEINE

For nearly two decades, numerous clinical trials have investigated the role of acetylcysteine for the prevention of contrast-associated acute kidney injury. The results of these trials and meta-analyses are highly divergent and inconclusive. Despite equipoise on its efficacy, acetylcysteine has been widely used in clinical practice because of its low cost, ease of use, and limited toxic effects. In the PRESERVE trial, oral acetylcysteine was administered at a dose of 1200 mg twice daily for 5 days, beginning on the day of angiography.[19] As compared with placebo, acetylcysteine was not associated with reductions in the rate of death, need for dialysis, or the rate of persistent impairment in kidney function at 90 days (4.6% with acetylcysteine and 4.5% with placebo; odds ratio, 1.02; 95% CI, 0.78 to 1.33; P=0.88) or in the rate of contrast-associated acute kidney injury (9.1% and 8.7%, respectively; odds ratio, 1.06; 95% CI, 0.87 to 1.28; P=0.58). On the basis of these findings, the routine administration of acetylcysteine is not recommended for the prevention of acute kidney injury or longer-term adverse events after angiographic procedures.

STATINS

The hypothesis that statins reduce the risk of contrast-associated acute kidney injury is based on their antiinflammatory and antioxidant properties. The PROMISS (Prevention of Radiocontrast Medium–Induced Nephropathy Using Short-Term High-Dose Simvastatin in Patients with Renal Insufficiency Undergoing Coronary Angiography) trial failed to show a difference between simvastatin and placebo with respect to a primary end point based on the mean peak increase in the plasma creatinine level within 48 hours after angiography in patients with chronic kidney disease.[67] Conversely, the PRATO-ACS (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients with Acute Coronary Syndrome) trial showed a significant reduction in rates of acute kidney injury and 30-day cardiovascular and renal events after PCI in patients treated with high-dose rosuvastatin (40-mg loading dose on admission followed by a maintenance dose of 20 mg per day) as compared with patients who did not receive statin treatment.[68]

Other trials and several meta-analyses have documented a benefit of prophylactic statins in patients undergoing PCI.[69,70] However, several of these trials have methodologic limitations — namely, small samples leading to limited statistical power to examine patient-centered outcomes. Further studies are needed to definitively clarify the role of prophylactic administration of high-dose statins. Nonetheless, because high-intensity statins are commonly indicated for atherosclerotic disease according to clinical practice guidelines, many patients undergoing procedures with contrast administration will have an indication for maintenance therapy with these agents.

OTHER PRACTICAL PREVENTIVE CONSIDERATIONS

Among patients identified as high risk, using the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium is advisable. Although a specific threshold definitively associated with contrast-associated acute kidney injury has not yet been determined, one approach is to limit the total volume to less than double the patient's baseline glomerular filtration rate.[71,72] There are insufficient data to support discontinuation of diuretics, angiotensin-converting–enzyme inhibitors, or angiotensin-receptor blockers. Stop-

ping potentially nephrotoxic agents, including nonsteroidal antiinflammatory medications, is appropriate. A preemptive temporary suspension of metformin therapy has been advocated, not because this medication augments the risk of kidney injury but rather out of concern about the development of lactic acidosis, should severe acute kidney injury occur. Given the prevalence of diabetes, the widespread use of metformin, and practical issues related to the temporary discontinuation of the medication, additional data are needed before firm, evidence-based recommendations can be provided regarding the discontinuation of metformin in patients undergoing contrast-enhanced procedures. Figure 3 depicts our recommended preventive strategies for patients undergoing angiographic procedures.

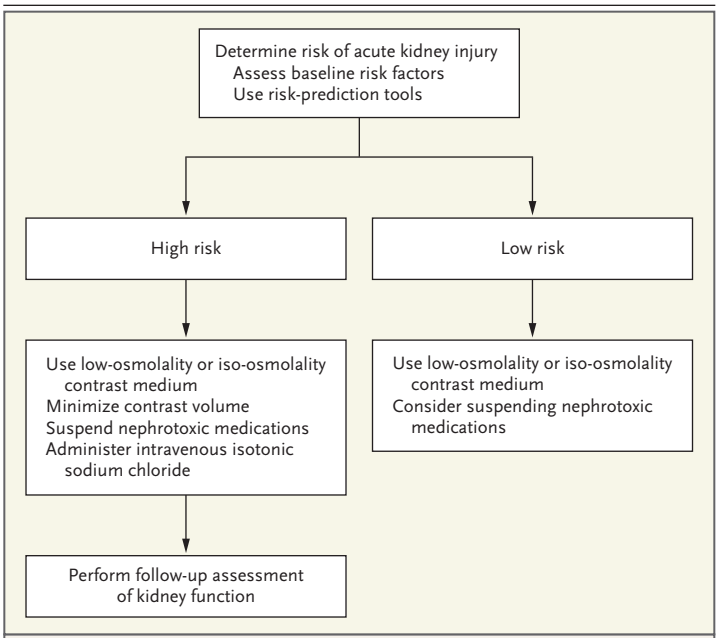


Figure 3. Approach to the Prevention of Contrast-Associated Acute Kidney Injury in Patients Undergoing Angiographic Procedures.

The most effective regimen of intravenous sodium chloride administration in patients at high risk for contrast-associated acute kidney injury has not been determined.

CONCLUSIONS

There have been incremental advances in our understanding of the pathophysiology of and risk factors for contrast-associated acute kidney injury. However, reliance on a definition based on small increments in the plasma creatinine level, which are frequently transient and nonspecific for contrast-induced damage, coupled with observational studies showing an association with serious, adverse outcomes without known cause, has limited meaningful progress in determining the clinical importance of this condition. Additional work is clearly needed to effectively address the ongoing controversy over the true toxic effects of contrast materials in current use, to determine whether there is any justification for limiting their use in patients at elevated risk for kidney injury, and to evaluate the possible survival benefit associated with preventing this iatrogenic condition.

The opinions expressed in this article are those of the authors and do not necessarily represent the views of the U.S. government or the Department of Veterans Affairs.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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