Prevention of Contrast-Induced Acute Kidney Injury

Case Study and Commentary, Steven D. Weisbord, MD, MSc, and Paul M. Palevsky, MD

ABSTRACT

- **Objective:** To review the risk factors, definition, pathophysiology, prevention, and adverse outcomes associated with the development of acute kidney injury resulting from iodinated contrast.
- **Methods:** Case presentation and evaluation of the medical literature.
- **Results:** Contrast-induced acute kidney injury (CIAKI) is characterized by the abrupt loss of kidney function following the intravascular administration of iodinated contrast media. Typically defined in clinical practice and research by increases in serum creatinine of ≥25% and/or ≥0.5 mg/dL within 2 to 4 days of contrast administration, CIAKI occurs in up to 10% to 15% of at-risk patients overall and as many as 30% or more of high-risk hospitalized patients. Underlying renal insufficiency is the principal risk factor for CIAKI, while diabetes mellitus significantly amplifies the risk in patients with baseline kidney disease. The principal intervention for the prevention of CIAKI in high-risk patients is the provision of intravenous fluids prior to and following the administration of iodinated contrast. The use of iso-osmolar or specific low-osmolar contrast agents also minimizes risk. N-acetylcysteine, a vasodilatory antioxidant, has been investigated in dozens of clinical trials and meta-analyses with conflicting results.
- **Conclusion:** CIAKI is a common iatrogenic condition that is associated with serious adverse outcomes. Knowledge of the key risk factors and data supporting the use of specific preventive interventions will inform the implementation of evidence-based care to minimize the incidence and potential sequelae of this iatrogenic condition.

CASE STUDY

Initial Presentation

A 67-year-old white male presents to his primary care provider complaining of 4 weeks of intermittent chest discomfort with exertion that is relieved by rest. He has a history of diabetes mellitus, hypertension, osteoarthritis, and chronic kidney disease. His medications include glipizide, aspirin, amlodipine, lisinopril, and over-the-counter ibuprofen as needed. His blood pressure is 142/78 mm Hg, lungs are clear to auscultation, and the remainder of the physical examination is unremarkable. An electrocardiogram demonstrates no acute abnormalities. Exercise stress testing reveals reversible ischemia in the lateral myocardial wall. The patient is referred for coronary angiography. Prior to the procedure, serological testing demonstrates a hemoglobin level of 12.1 g/dL, serum creatinine (SCr) of 1.9 mg/dL, and blood urea nitrogen of 44 mg/dL. His estimated glomerular filtration rate is 36 mL/min/1.73m².

- **What are the risk factors for contrast-induced acute kidney injury?**

CIAKI rarely develops in the absence of specific risk factors (Table 1). Underlying impairment in kidney function is the single most important risk factor for CIAKI, with lower levels of kidney function associated with increasing levels of risk [1]. In a study of 378 hospitalized patients undergoing angiography, D’Elia et al found underlying renal impairment to be the sole risk factor for CIAKI [2]. Among patients with mild to moderate underlying renal insufficiency, the incidence of CIAKI is typically less than 10%, while the incidence increases considerably in patients with more severe levels of renal dysfunction. Conversion of SCr to estimated glomerular filtration rate (eGFR), which is now performed automatically by many laboratories, is important to estimating level of baseline kidney function as normal or mildly el-
Elevated SCr values may reflect significant underlying renal impairment in women, the elderly, and patients with diminished muscle mass. While diabetes mellitus in the setting of normal kidney function is not believed to be a significant risk factor for CIAKI, it significantly increases the risk in patients with underlying renal dysfunction [3–5]. This was well characterized by Rudnick et al in a trial of 1196 patients undergoing coronary angiography [4]. CIAKI occurred in none of the participants without diabetes or renal insufficiency and in just 0.6% of those with diabetes and normal kidney function [4]. However, in patients with baseline kidney disease, 6% of nondiabetics and 20% of diabetics developed CIAKI.

Patients with absolute intravascular volume depletion from gastrointestinal, renal or other losses, as well as those with effective intravascular volume depletion from heart or liver failure are also at increased risk of CIAKI [6]. In both clinical states, there is increased reliance on vasodilatory prostaglandins to maintain renal perfusion. The administration of iodinated contrast, which is vasoconstrictive, in these settings can overwhelm the capacity of vasodilatory prostaglandins and nitric oxide to help maintain adequate renal blood flow leading to renal ischemia [6–8]. Similarly, use of nephrotoxic medications at the time of contrast administration such as nonsteroidal anti-inflammatory medications, which inhibit vasodilatory prostaglandins in the kidney, can increase the risk for CIAKI [9].

A series of procedure-related factors also increase the risk for CIAKI. In some studies, there is a direct relationship between higher volumes of contrast administered and increased risk for CIAKI [10–12]. Although a specific threshold volume of contrast above which the risk for CIAKI increases substantially has not been definitively established, multiple serial procedures or procedures requiring large volumes of contrast appear to pose an increased risk. Studies have examined a maximum contrast dose (5 × body weight [kg])/SCr) and demonstrated increased risk for CIAKI and adverse outcomes using this threshold [13,14]. Similarly, higher doses of iodine have been shown to increase the risk for CIAKI, which has led to the development of formulas that consider the dose of iodine to estimate risk. However, the relative importance of iodine dose compared to overall volume of contrast requires further investigation. Type of contrast agent has also been strongly associated with risk for CIAKI. Iodinated contrast media used in clinical practice more than 2 decades ago were ionic compounds with osmolalities up to 5 to 8 times greater than blood (approximately 1500–2000 mOsm/kg). The subsequent development of “low-osmolal” contrast with osmolalities of 500–800 mOsm/kg was associated with lower rates of CIAKI [4,15]. Most recently, iso-osmolal ioxitano has been compared to low osmolal agents in clinical trials and meta-analyses with conflicting results (see section on prevention).

Direct comparisons of the incidence of CIAKI following angiography and contrast-enhanced computed tomography have been scarce. In a study of 660 patients with CKD, Weisbord et al demonstrated that CIAKI, defined by an increase in SCr ≥ 25%, was more than twice as common following noncoronary angiography (13.2%) than after contrast-enhanced computed tomography (6.5%) [16]. However, these analyses did not adjust for potential confounders, including diabetes mellitus, heart failure, severity of CKD, or differential utilization of preventive interventions such as intravenous (IV) fluids. Differences in such factors across procedure types may account for the higher observed rates of CIAKI following angiography and may underlie the general belief that procedures involving intra-arterial contrast administration are associated with a higher risk of CIAKI than procedures that utilize intravenous injection.

What is the definition of and pathophysiology underlying CIAKI?

While the serological criteria used to define CIAKI vary across studies, the most commonly employed definition is an increase in SCr of ≥ 0.5 mg/dL and/or ≥ 25% within 48 to 96 hours of contrast exposure [17–19]. The

Table 1. Principal Risk Factors for CIAKI

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<td>• Underlying renal dysfunction</td>
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<td>• Diabetes mellitus in setting of chronic kidney disease</td>
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<td>• Absolute volume depletion</td>
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<td>• Effective volume depletion (eg, congestive heart failure)</td>
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<td>• High volume of contrast</td>
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<td>• Use of high-osmolal contrast</td>
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<td>• Multiple sequential procedures with contrast</td>
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![CASE-BASED REVIEW](Image)
CONTRAST-INDUCED ACUTE KIDNEY INJURY

Acute Kidney Injury Network recently defined AKI of any etiology based on an increase in SCr of \( \geq 0.3 \) mg/dL or 50%. There are limited data on the application of this definition to patients sustaining contrast-associated renal injury. Another classification of AKI (RIFLE) is based on various stages of disease ranging from “Risk” to “Failure” based on progressively more severe decrements in renal function. Few patients with CIAKI reach the more severe levels of renal injury based on this classification scheme. In addition, there are growing data that urinary biomarkers including neutrophil gelatinase-associated lipocalin (NGAL) and liver fatty acid binding protein (L-FABP) are able to detect renal injury before elevations in SCr occur. However, the widespread use of these biomarkers in clinical practice to diagnose CIAKI will require further validation studies.

Three principal pathophysiological processes underlie the nephrotoxicity of iodinated contrast media (Figure 1) [20]. First, the intravascular administration of iodinated contrast leads to intense vasoconstriction, which in the outer portion of the renal medulla results in mismatch of oxygen supply and demand, ischemia of epithelial cells, and tubular injury. Second, after being filtered at the glomerulus and transiting the renal tubular space, iodinated contrast causes direct toxicity to renal tubular epithelial cells. Third, the administration of iodinated contrast leads to the generation of reactive oxygen species (ROS), which exacerbate renal tubular epithelial cell injury.

**Figure 1. Pathophysiology of CIAKI.**

The incidence of CIAKI depends on the underlying risk factors in the patient population being studied and the criteria used to define renal injury. An observational cohort study by Weisbord and colleagues enrolled patients with baseline eGFR less than 60 mL/min/1.73m\(^2\) undergoing nonemergent angiography or computed tomography and demonstrated that the incidence of CIAKI, defined by an increase in SCr of \( \geq 25\% \), was 13.2\% following noncoronary angiography, 8.5\% following coronary angiography, and 6.5\% following computed tomography [16]. Using more robust increments in SCr to define CIAKI resulted in considerably lower rates of renal injury, with less than 1\% of patients overall experiencing a rise in SCr of \( \geq 1.0 \) mg/dL. In a recent observational study of 1111 hospitalized patients, the incidence of CIAKI, defined as an increase in SCr of \( \geq 0.5 \) mg/dL within 1 to 5 days, was as high as 44\% among patients with baseline renal insufficiency and concomitant diabetes [21]. Thus, the incidence of CIAKI is highly dependent on the patient population, clinical setting, and definition of CIAKI.

**Case Continued**

Prior to angiography, the interventional cardiologist contacts the patient to notify him that he is at increased risk for CIAKI based on underlying chronic kidney disease (ie, eGFR 36 mL/min/1.73m\(^2\)) and diabetes. He estimates that his risk for CIAKI is approximately 5\% to 10\% and informs the patient that preventive interventions will be implemented to minimize the risk of CIAKI.
Procedures that utilize intravascular contrast are commonly scheduled in advance, providing sufficient time to implement preventive measures. Moreover, patients at elevated risk for CIAKI are easily identifiable by the aforementioned clinical risk factors, which facilitates the identification of individuals most likely to derive benefit from preventive care. Research to identify preventive strategies for CIAKI has focused on 4 principal approaches: (1) use of contrast agents associated with less nephrotoxicity; (2) expansion of the vascular space with the periprocedural administration of IV fluids; (3) implementation of pharmacologic agents to neutralize the nephrotoxic effects of contrast media; and (4) provision of periprocedural renal replacement therapy to remove contrast from the circulation.

Use of the Least Nephrotoxic Contrast Media

Iodinated contrast agents are either monomers containing a single triiodobenzene ring or dimers with 2 triiodobenzene rings (Figure 2) [22]. The initial contrast agents used in clinical practice were ionic and “high-osmolar” with osmolalities of approximately 1500 mOsm/kg to 2000 mOsm/kg. The next generation of contrast media was termed “low-osmolar” because their osmolalities were considerably lower than the original high-osmolar compounds. Since most low-osmolar contrast media (LOCM) are nonionic and do not dissociate in solution, an equivalent dose of iodine is provided with approximately half the osmolar load compared to the high-osmolar agents. Most recently, nonionic, iso-osmolar contrast media (IOCM) have been developed, which have osmolalities comparable to that of blood. However, as the osmolality of newer agents has decreased, their viscosity has increased.

Multiple studies have investigated the relationship between contrast agent osmolality and risk for CIAKI. Early studies focused on comparing high and low osmolar agents [4,15]. Following the performance of a series of small studies, Rudnick et al reported the results of the Iohexol Cooperative Study, a multicenter clinical trial comparing high-osmolar diatrizoate with low-osmolar iohexol in 1196 patients undergoing coronary angiography [4]. Overall, CIAKI was less common with iohexol than diatrizoate (3.2% v. 7.1%, *P = 0.002*), including among the subset of patients with both diabetes mellitus and baseline renal impairment. Using data from this and several other trials, Barrett and Carlisle published a meta-analysis demonstrating a lower risk of CIAKI with low-osmolar contrast compared to high-osmolar agents (odds ratio [OR], 0.61; 95% CI, 0.48–0.77) with the benefit specifically noted in patients with pre-existing renal impairment and those receiving intra-arterial contrast administration [15]. These studies helped establish a sound evidence-basis for the preferential use of low-osmolar contrast in patients with impaired baseline kidney function.

More recently, clinical trials have compared LOCM with iso-osmolar iodoxanol. Although some studies demonstrated a lower incidence of CIAKI associated with iodoxanol than with certain LOCM (ie, iohexol, ioxaglate), the results were inconsistent across studies [23–30]. Meta-analyses suggest that while iodoxanol may be associated with a lower risk of CIAKI than certain specific low-osmolar agents (eg, iohexol and ioxaglate), this benefit is not observed across the entire spectrum of LOCM [31–35]. Guidelines issued by the American College of Cardiology/American Heart Association in 2009 recommended the use of IOCM or LOCM exclusive of iohexol and ioxaglate in at-risk patients [36]. However, more recent guidelines conclude that there are insufficient data to recommend the preferential use of IOCM or a specific LOCM in patients with chronic kidney disease undergoing angiography [37]. Larger, adequately powered trials will be needed to further clarify the comparative effects of IOCM and LOCM.

Intravenous Fluids

Intravascular volume expansion with IV crystalloid is believed to have 2 actions that protect against the development of CIAKI. First, IV fluids may dampen the vasoconstrictive effects of contrast on the renal medulla due to the suppression of vasopressin, inhibition of the renin-angiotensin axis, and augmentation in the synthesis of vasodilatory renal prostaglandins [38]. Second, IV fluids are hypothesized to decrease the concentration and viscosity of contrast media in the tubular lumen, which may attenuate the direct toxic effect of contrast agents on renal tubular epithelial cells [38]. Findings from multiple randomized clinical trials form the current evidence basis for the use of IV fluids to prevent CIAKI and inform our understanding of the effect of IV fluid composition. In a trial conducted nearly 20 years ago, Solomon et al
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randomized patients with CKD undergoing coronary angiography to receive IV 0.45% NaCl alone or in combination with IV mannitol (25 g) or furosemide (80 mg) [39]. The incidence of CIAKI was lower among patients who received IV fluids alone (11%) than patients who received IV fluid plus mannitol (28%) or furosemide in addition to IV fluids (40%). While often cited as demonstrating the benefit of IV crystalloid, it should be recognized that this study did not have a control arm of patients who did not receive IV fluids. Trivedi et al subsequently demonstrated the benefit of IV fluid in a small clinical trial of patients undergoing non-emergent coronary angiography [40]. Patients were randomized to receive either IV isotonic saline for 12 hours prior to and 12 hours following angiography or unrestricted oral fluids. The study was stopped at an interim analysis when the rate of CIAKI was found to be markedly higher with oral fluids compared to the IV fluid (34.6% vs. 3.7%, \( P = 0.005 \)). The effect of IV fluid tonicity on the development of CIAKI was assessed by Mueller et al in a study in which low-risk patients undergoing coronary angiography were randomized to receive 0.45% saline or 0.9% saline at the time of the procedure [41]. CIAKI developed more frequently in patients who received half-isotonic saline compared to those who received isotonic saline (2% vs 0.7%, \( P = 0.04 \)).

Recent research has focused on identifying the preferred anion to sodium; specifically, comparing isotonic sodium bicarbonate (bicarbonate) with isotonic sodium chloride. One of the pathophysiological mechanisms believed to contribute to the development of CIAKI is the generation of reactive oxygen species (ROS) in the kidney (Figure 1). Moreover, key clinical risk factors for CIAKI, including CKD, diabetes, intravascular volume depletion, and heart failure are also associated with increased ROS generation [42–45]. In animal studies, the generation of ROS in the kidney is enhanced in acidic urine and attenuated by urinary alkalinization [46]. Thus, it is hypothesized that IV sodium bicarbonate mitigates the risk for CIAKI through urinary alkalinization, blunting the generation of ROS. Over the past 8 years, multiple clinical trials comparing IV isotonic bicarbonate with IV isotonic saline for the prevention of CIAKI have been published, some demonstrating a lower incidence of CIAKI with bicarbonate and others showing no significant differences (Table 2) [47–56].

The disparate results of clinical trials have led to a proliferation of systematic reviews and meta-analyses comparing the effectiveness of bicarbonate and saline, with most, but not all, reporting a reduction in CIAKI with bicarbonate [57–63]. However, these meta-analyses also describe substantial study heterogeneity and publication bias, which limit the capacity to draw definitive conclusions. Most cite the need for large, adequately powered, randomized clinical trials comparing the effects of these 2 IV fluids and many suggest the need for such a study to be designed to detect differences in patient-centered outcomes rather than focusing on the small changes in SCr used to define CIAKI [59,61,63–66]. Additional studies are ongoing and planned [67,68]. However, until such adequately powered clinical trials are completed, it is clinically appropriate to utilize either isotonic sodium bicarbonate or isotonic sodium chloride for the prevention of CIAKI in at-risk patients. Of note, recent studies have examined the efficacy of a device that achieves high urine output matching the volume of IV fluid administered to the periprocedural urine output, and suggested potential
benefit to this approach [69,70]. However, while the device matches fluid volumes, it is probable that sodium balance is not matched as the urine composition is likely to be hypotonic relative to saline, leading to net positive sodium balance and confounding the interpretation of the benefits of this device. Until larger, adequately powered studies of this device are performed, it is premature to recommend its routine use.

**Pharmacological Agents**

A myriad of pharmacological agents have been tested for their capacity to reduce renal injury associated with the administration of iodinated contrast media. Unfortunately, most have demonstrated no clear benefit and in some cases, have been shown to be potentially deleterious. Studies have failed to demonstrate a reduction in CIAKI with furosemide, dopamine, fenoldopam, calcium channel blockers, and mannitol and in some instances have shown an increased risk of renal injury and other adverse effects [39,71–73]. Equipoise persists on the benefit of natriuretic peptides, aminophylline, and theophylline, statins, and ascorbic acid, studies of which have demonstrated mixed results. Given the potential safety concerns with the widespread use of natriuretic peptides, aminophylline, and theophylline, it is premature to recommend their routine use [74].

The singular pharmacological agent that has been the focus of the greatest number of clinical trials for prevention of CIAKI has been N-acetylcysteine (NAC). NAC scavenges ROS, reduces the depletion of glutathione, and stimulates the production of vasodilatory mediators such as nitric oxide. Tepel et al first described the efficacy of NAC for the prevention of CIAKI more than 10 years ago [75]. In this trial, 83 patients undergoing computed tomography were randomized to receive 600 mg of oral NAC or oral placebo twice daily on the day prior to and the day of the procedure. Significantly fewer trial participants who received NAC developed CIAKI than patients who received placebo (2% vs 21%, \(P = 0.01\)). Subsequently, a multitude of trials of NAC have been published with widely varying results (Table 3) [76–85]. While some trials demonstrated a reduction in the incidence of CIAKI with NAC, others showed no benefit. However, there are key methodological limitations to these studies. First, most have postulated large yet biologically implausible effect sizes, leading to the

<table>
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<th>Positive studies</th>
<th>Number of Patients</th>
<th>Baseline SCr (mg/dL)</th>
<th>Definition of 1º Outcome</th>
<th>Frequency of CIAKI Bicarbonate</th>
<th>Frequency of CIAKI Saline</th>
<th>Assumed Effect Size of Bicarbonate</th>
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<tr>
<td>Briguori et al</td>
<td>219</td>
<td>2.0</td>
<td>↑ SCr ≥ 25%</td>
<td>1.9%</td>
<td>9.9%</td>
<td>86%</td>
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<td>Masuda et al</td>
<td>59</td>
<td>1.3</td>
<td>↑ SCr ≥ 0.5mg/dL or ≥ 25%</td>
<td>6.6%</td>
<td>34.5%</td>
<td>85%</td>
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<tr>
<td>Merten et al</td>
<td>119</td>
<td>1.7–1.9</td>
<td>↑ SCr ≥ 25%</td>
<td>1.7%</td>
<td>13.6%</td>
<td>66%</td>
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<tr>
<td>Ozcan et al</td>
<td>176</td>
<td>1.4</td>
<td>↑ SCr ≥ 0.5mg/dL or ≥ 25%</td>
<td>4.2%</td>
<td>16.6%</td>
<td>NR</td>
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<tr>
<td>Pakfetrat et al</td>
<td>192</td>
<td>1.1</td>
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<td>4.2%</td>
<td>12.5%</td>
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<tr>
<td>Recio-Mayoral et al</td>
<td>111</td>
<td>1.0</td>
<td>↑ SCr ≥ 0.5mg/dL</td>
<td>1.8%</td>
<td>21.8%</td>
<td>85%</td>
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<td>Maioli et al</td>
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<td>Vasheghani et al†</td>
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*Three definitions of CIAKI assessed; differences between bicarbonate and saline based on ↑ SCr ≥ 0.3 mg/dL.
†Bicarbonate administered as 75 mL of 8.4% sodium bicarbonate added to 1 L isotonic saline (ie, hypertonic bicarbonate).
enrollment of very small numbers of patients and significantly limiting their statistical power. Second, some studies included patients at low risk for CIAKI, resulting in lower than expected event rates and mitigating differences between treatment arms. This is of particular concern in the interpretation of the ACT trial, the largest randomized controlled trial of NAC for the prevention of CIAKI [86].

In this study of over 2300 patients that did not demonstrate any reduction in the risk of CIAKI with NAC treatment, only a small minority of patients had underlying CKD. This significantly diminished the risk profile of the study population, leaving the question of whether NAC is beneficial in high-risk patients unanswered. Finally, most trials used small changes in SCr as the primary endpoint.

<table>
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<th>Table 3. Trials of N-acetylcysteine</th>
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<tr>
<td><strong>NAC Dose</strong></td>
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<td><strong>Positive studies</strong></td>
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<td>Baker et al</td>
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<td>Sandhu et al</td>
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<td>Webb et al</td>
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NR = not reported.

*150 mg/kg IV x 1 hr pre and 50 mg/kg IV x 4 hr post-angiography.
†2 NAC groups: standard dose = 600 mg IV and 600 mg po x 4; high dose = 1200 mg IV and 1200 mg po x 4.
‡2000 mg po either x 2 or x 3.
and did not systematically track more clinically meaningful outcomes such as need for dialysis, death, rehospitalization, or progressive kidney injury. Of note, a small number of studies have compared higher to lower dose NAC and demonstrated a benefit to higher doses [87,88]. It remains unclear whether higher doses of NAC are required to realize any clinical benefit to this intervention.

The incongruent clinical trial findings resulted in the publication of multiple systematic reviews and meta-analyses [88,92]. Kelly et al. studied 26 trials that included 3393 patients and demonstrated a 38% reduction in the risk of CIAKI associated with NAC (relative risk, 0.62; 95% CI, 0.44–0.88). Nearly simultaneously, Gonzalez et al. published a meta-analysis of 22 trials and 2746 patients that reported no clear benefit to NAC. A recent meta-analysis by Trivedi et al. reported a reduction in the risk for CIAKI with high-dose NAC. Thus, the conclusions of multiple meta-analyses of NAC are as conflicting and inconclusive as the primary clinical trials.

It is also important to note that certain medications likely increase the risk for CIAKI, particularly among patients with other risk factors. Most notably, selective and nonselective nonsteroidal anti-inflammatory agents, which inhibit the production of vasodilatory prostaglandins in the kidney, likely increase the risk for CIAKI if taken by at-risk patients around the time of contrast administration. It should be noted that certain expert recommendations for the prevention of CIAKI suggest discontinuation of metformin. Metformin is not nephrotoxic, but increases the risk for potentially serious lactic acidosis in the setting of acute kidney injury. While this complication is quite rare, discontinuing metformin at the time of contrast administration in patients at increased risk for CIAKI is advisable until a post-procedure determination has been made that renal injury has not occurred. There are no sound data to support the discontinuation of angiotensin receptor blockers, angiotensin converting enzyme inhibitors, or chronic diuretics prior to contrast administration for the purpose of limiting the risk of CIAKI.

**Hemodialysis/Hemofiltration**

Because of their molecular characteristics, iodinated contrast media are efficiently cleared from the circulation by renal replacement therapies including hemodialysis, resulting in studies examining the effect of prophylactic renal replacement therapy in reducing the risk for CIAKI. Lee et al. demonstrated that patients with CKD randomly assigned to receive hemodialysis at the time of coronary angiography experienced a smaller decrement in creatinine clearance and less frequent requirement for chronic hemodialysis compared to patients who did not receive prophylactic hemodialysis [94]. However, the small sample size of this study, inaccuracies inherent in the measurement of creatinine clearance based on 24-hour urine collection (the primary study endpoint), and a dearth of trial participants who required chronic hemodialysis preclude meaningful conclusions from this trial. Most other trials conducted over the past 2 decades demonstrated either no benefit or a greater incidence of CIAKI in patients who received prophylactic hemodialysis [95–100]. Owing to the lack of sound evidence supporting its benefit, the need for vascular access, and the risks and costs associated with an invasive treatment like hemodialysis, this approach to the prevention of CIAKI is not recommended.

Continuous renal replacement therapy (CRRT) also removes iodinated contrast from the circulation, although less rapidly than conventional hemodialysis therapy. Marenzi et al. investigated prophylactic continuous venovenous hemofiltration (CVVH) for the prevention of CIAKI in 2 studies and reported a decrease in the incidence of CIAKI and death [101,102]. However, the primary endpoint in these trials was short-term small increases in Scr following contrast administration, which is directly affected by hemofiltration, and therefore of limited utility. With limited sound evidence of a benefit along with issues related to cost and potential risks, preemptive use of CRRT to prevent the development of CIAKI or its sequelae is not recommended.

**Summary**

At the current time, the approach to the prevention of CIAKI in patients at increased risk involves a series of steps (Figure 3). First, if possible, use of an alternative imaging procedure that does not require intravascular contrast should be considered. If iodinated contrast is required, IV isotonic fluid should be administered prior to and following the procedure. The optimal duration or rate of administration of IV fluids has not been conclusively determined. In patients undergoing outpatient or urgent procedures, administration of IV isotonic saline or sodium bicarbonate at a rate of 3 mL/kg/hr for 1 hour prior to the procedure and 1 to 1.5 mL/kg/hr for 4 to 6 hours following the procedure is a reasonable and practical approach. For inpatients undergoing non-urgent studies, administration of IV fluids at a rate of 1 mL/kg/hr for 12 hours prior to

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and 12 hours following the procedure is consistent with the current standard of care. The provision of NAC in a dose of 1200 mg by mouth twice daily for 2 days beginning on the day of the procedure is inexpensive and safe, yet should not be used in lieu of IV fluids. Concomitant nonsteroidal anti-inflammatory agents should be discontinued and IOCM or LOCM, perhaps other than iohexol and ioxaglate should be used in the lowest possible dose. SCr should be assessed 2 to 4 days following the procedure to assess for the development of CIAKI. There are recent data suggesting that medical centers with standardized protocols for the prevention of CIAKI have lower event rates than centers without established strategies [103].

Case Continued

Based on the currently available evidence, the patient was instructed to discontinue use of ibuprofen at the time of the procedure. He was prescribed oral NAC in a dose of 1200 mg twice daily for 2 days beginning on the day of angiography and based on his weight of 80 kg, an infusion of isotonic IV sodium bicarbonate was administered at a rate of 240 mL over 1 hour prior to and 80 mL/hr for 6 hours following the procedure. Coronary angiography was performed using 75 mL of low-osmolal iopamidol and demonstrated a 90% stenosis of the circumflex artery, which led to percutaneous intervention. Three days following the procedure, he had outpatient testing of SCr, which revealed a value of 2.8 mg/dL. He reported no symptoms or change in urine output.

In multiple studies, CIAKI is associated with increased short-term mortality risk [3,104–107]. In a retrospective analysis, Levy et al demonstrated that CIAKI was independently associated with increased in-hospital death (OR, 5.5; P < 0.001) [104]. McCullough et al studied 1826 patients who underwent percutaneous coronary intervention and found a considerably higher incidence of in-hospital mortality among patients who developed CIAKI than in subjects without CIAKI (7.1% vs 1.1%) [3]. CIAKI that required renal replacement therapy was associated with a markedly higher incidence of in-hospital mortality (35.7%). Such retrospective studies are susceptible to ascertainment bias and to the issue of missing data. However, prospective studies mirror these findings [49,78]. As part of a clinical trial, Marenzi et al found that patients with CIAKI experienced a significantly increased incidence of in-hospital mortality compared with patients without CIAKI (26% vs 1.4%, P < 0.001) [78]. An even more recent trial of patients undergoing coronary angiography by Maioli et al demonstrated that in-hospital mortality among patients who developed CIAKI (defined by an increase in SCr of ≥ 0.5 mg/dL) was markedly higher than among patients who did not develop CIAKI (11.1% vs 0.2%, P = 0.001) [49]. Thus, data from observational studies and clinical trials support an association of small post-angiography decrements in renal function with short-term mortality.

Several but not all retrospective studies and clinical trials also document an association of CIAKI with prolonged hospitalization and increased short-term costs [105,108–110]. Bartholomew et al demonstrated that patients who developed CIAKI following percutaneous intervention...
were 15 times more likely to have their hospitalization prolonged in excess of 4 days [108]. Adolph and colleagues reported that patients with post-angiography CIAKI remained in the hospital an average of 2 days longer than patients without CIAKI [56]. This extended length of stay translates into increased costs [110,111]. In a study of 598 diabetics with CKD undergoing coronary angiography, Weisbord et al demonstrated that CIAKI was independently associated with a two-fold increase in hospital-related costs [110,111]. A decision analysis by Subramanian et al found that CIAKI is associated with hospital-related costs greater than $10,300 [109]. Estimating that 110,000 cases of angiography-associated CIAKI occur each year in the United States, the cumulative annual cost of CIAKI may be in excess of $1.1 billion [109,112].

**What are the long-term adverse outcomes associated with CIAKI?**

CIAKI is also associated with serious adverse long-term outcomes [113–115]. Solomon et al demonstrated an increased risk of death, stroke, myocardial infarction, or end-stage renal disease requiring renal replacement therapy at 1-year of follow up among patients who experienced CIAKI following angiography [114]. CIAKI is also associated with acceleration in the progression of CKD. In a series of 78 patients with CKD, Goldenberg et al found that patients with transient post-angiography CIAKI defined by an increase in SCr of ≥ 25% or ≥ 0.5 mg/dL experienced a larger decrement in eGFR at 2 years of follow up compared with patients without CIAKI (Δ eGFR = − 20 ± 11 mL/min/1.73 m² v. − 6 ± 16 mL/min/1.73 m², P = 0.02) [113]. James et al reported that patients with mild CIAKI following coronary angiography had increased odds of a persistent reduction in kidney function at 90 days (adjusted OR, 4.74; 95% CI, 3.92–5.74), while severe CIAKI was associated with dramatically increased odds of persistent impairment in renal function at 90 days following angiography (adjusted OR, 17.3; 95% CI, 12.0–24.9) [116]. This study also demonstrated that CIAKI was associated with an accelerated decline in kidney function, defined as a loss of eGFR >4 mL/min/1.73 m² per year over up to 3 years of follow up and an increased odds of end-stage renal disease (OR, 13.8; 95% CI, 7.4–25.9) [116]. Collectively, these findings indicate that CIAKI, defined by small decrements in kidney function, is associated with adverse long-term outcomes and more compromised renal function months to years following angiography.

It should be noted that studies demonstrating an association of CIAKI with adverse short- and long-term outcomes do not establish the causal nature of these associations. Determining whether CIAKI is a mediator of serious adverse downstream events or simply a marker of higher-risk patients with greater baseline comorbidity will require large, adequately powered clinical trials that are designed to determine whether the prevention of CIAKI translates into a reduction in adverse patient-centered events.

**Case Follow-up**

Repeat SCr testing 5 days following angiography revealed a value of 2.2 mg/dL. Two weeks following angiography, the patient’s SCr was 2.1 mg/dL. He was referred for outpatient nephrology follow-up with the recognition that he may be at increased risk for more rapid progression of underlying chronic kidney disease as a result of experiencing an episode of CIAKI.

**CONCLUSION**

CIAKI remains a common complication of contrast-enhanced imaging procedures. Recognition of the principal risk factors, including impaired baseline kidney function, diabetes with renal insufficiency, and absolute or effective intravascular volume depletion, permits early identification of patients at greatest risk and informs the implementation of evidence-based preventive care. The provision of isotonic IV fluids prior to and following the administration of iodinated contrast remains the cornerstone of prevention. Use of the least nephrotoxic contrast agent in the lowest possible volume, administration of NAC, and discontinuation of concomitant nephrotoxic agents are also appropriate steps to reduce the risk. The importance of implementing these measures in at-risk patients is underscored by the growing number of studies demonstrating that CIAKI is associated with serious, adverse short- and long-term outcomes.

*Note: The views expressed in this article are those of the authors and do not represent the views of the Department of Veterans Affairs.*

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CONTRAST-INDUCED ACUTE KIDNEY INJURY

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