Journal of the American College of Cardiology Vol. 51, No. 15, 2008

ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.12.035

STATE-OF-THE-ART PAPER

Contrast-Induced Acute Kidney Injury

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Cardiac angiography and coronary/vascular interventions depend on iodinated contrast media and consequently pose the risk of contrast-induced acute kidney injury (AKI). This is an important complication that accounts for a significant number of cases of hospital-acquired renal failure, with adverse effects on prognosis and health care costs. The epidemiology and pathogenesis of contrast-induced AKI, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies are discussed in this report. An advanced algorithm is suggested for the risk stratification and management of contrast-induced AKI as it relates to patients undergoing cardiovascular procedures. Contrast-induced AKI is likely to remain a significant challenge for cardiologists in the future because the patient population is aging and chronic kidney disease and diabetes are becoming more common. (J Am Coll Cardiol 2008;51:1419–28) © 2008 by the American College of Cardiology Foundation

Contrast-induced acute kidney injury (AKI) is an important complication in the use of iodinated contrast media, which accounts for a significant number of cases of hospital-acquired AKI (1–3). This iatrogenic complication has been a subject of concern to cardiologists in recent years because of its adverse effect on prognosis and addition to health care costs. At the same time, many hospitalized patients have compromised renal function (4,5), which is the most important risk factor for contrast-induced AKI. This report is largely based upon data from the Contrast-Induced Nephropathy (CIN) Consensus Working Panel, an international multidisciplinary group convened to address the challenges of contrast-induced AKI whose findings were published in 2006 (6–12).

Evaluating the Literature on Contrast-Induced AKI

The CIN Consensus Working Panel comprised 2 radiologists, 2 cardiologists, and 2 nephrologists practicing in Europe and the U.S. At the first meeting in November 2004, the overall scope and strategy for the project were agreed upon and at the second in September 2005, the Working Panel reviewed and discussed all of the evidence and developed a series of consensus statements. A systematic search of the literature was undertaken to identify all references relevant to the subject of contrast-induced AKI, as a result of which 865 potentially relevant studies were identified and reviewed. The results of the literature search were used to compile reviews covering the epidemiology and pathogenesis of AKI, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies (6–12). After reviewing all of the evidence, a series of consensus statements were developed (Table 1) (13).

Epidemiology and Prognostic Implications of Contrast-Induced AKI

Incidence. The reported incidence of contrast-induced AKI varies widely across the literature, depending on the patient population and the baseline risk factors. Moreover, as with any clinical event, the incidence also varies depending on the criteria by which it is defined. Contrast-induced AKI is typically defined in the recent literature as an increase in serum creatinine (SCr) occurring within the first 24 h after contrast exposure and peaking up to 5 days afterwards. In most instances, the rise in SCr is expressed either in absolute terms (0.5 to 1.0 mg/dl) or as a proportional rise in SCr of 25% or 50% above the baseline value. The most commonly used definition in clinical trials is a rise in SCr of 0.5 mg/dl or a 25% increase from the baseline value, assessed at 48 h after the procedure. The European Society of Urogenital Radiology defines contrast-induced AKI as impairment in renal function (an increase in SCr by >0.5 mg/dl or >25% within 3 days after intravascular administration of contrast medium, without an alternative etiology) (14). The Acute Kidney Injury Network definition is a rise in SCr ≥0.3 mg/dl with oliguria, which is compatible with previous definitions and may be a new standard to follow.

The best indication of the healthcare impact of contrast-induced AKI comes from large studies of hospital patients. The frequency of contrast-induced AKI has decreased over

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Manuscript received August 29, 2007; revised manuscript received December 10, 2007, accepted December 10, 2007.

JACC Vol. 51, No. 15, 2008
April 15, 2008:1419–28

Abbreviations and Acronyms

AKI = acute kidney injury
CIN = contrast-induced nephropathy
CKD = chronic kidney disease
CK-MB = creatine kinase-myocardial band
Cr = creatinine
DM = diabetes mellitus
eGFR = estimated glomerular filtration rate
HOCM = high-osmolal contrast media
IOCM = iso-osmolal contrast media
LOCM = low-osmolal contrast media
MI = myocardial infarction
NAC = N-acetylcysteine
PCI = percutaneous coronary intervention

the past decade from a general incidence of ~15% to ~7% of patients (15). This is due to a greater awareness of the problem, better risk prevention measures, and improved iodinated contrast media with less renal toxicity. However, many cases of contrast-induced AKI continue to occur because of the ever-increasing numbers of procedures requiring contrast. Nash et al. (3) reported that radiographic contrast media were the third most common cause of hospital-acquired renal failure (after decreased renal perfusion and nephrotoxic medications) and were responsible for 11% of cases.

It has been recognized for some time that the risk of death is increased in patients developing contrast-induced AKI (16–20). In a large retrospective study of over 16,000 hospitalized patients undergoing procedures requiring iodinated contrast, a total of 183 subjects developed contrast-induced AKI (defined as a 25% increase in SCr) (21). The risk of death during hospitalization was 34% in subjects who developed contrast-induced AKI compared with 7% in matched control subjects who had received contrast medium but did not develop contrast-induced AKI. Even after adjusting for comorbid disease, patients with contrast-induced AKI had a 5.5-fold increased risk of death (21). The high risk of in-hospital death associated with contrast-induced AKI was also documented in a retrospective analysis of 7,586 patients, of whom 3.3% developed contrast-induced AKI after exposure to contrast medium. Among the patients who developed contrast-induced AKI, the in-hospital death rate was 22% compared with only 1.4% in patients who did not develop AKI (22). The mortality rates at 1 year after development of contrast-induced AKI (12.1%) and at 5 years (44.6%) were higher compared with rates of 3.7% and 14.5%, respectively, in patients who did not develop contrast-induced AKI ($p < 0.001$), indicating that the increased risk of death persisted in the long term. A further study confirmed the high mortality in patients who develop contrast-induced AKI, especially in those who require dialysis: the hospital mortality was 7.1% in contrast-induced AKI patients and 35.7% in patients who required dialysis. By 2 years, the mortality rate in patients who required dialysis was 81.2% (17). Contrast-induced AKI (defined as an increase ≥25% in SCr) occurred in 37% of 439 patients with renal impairment (baseline SCr ≥1.8 mg/dl) undergoing percutaneous coronary intervention (PCI) (23). In this group, the hospital mortality rate was 14.9% compared with 4.9% in patients without contrast-induced AKI ($p = 0.001$). The cumulative 1-year mortality rates were 37.7% and 19.4%, respectively. The 1-year mortality was 45.2% for patients with contrast-induced AKI requiring dialysis and 35.4% for those with contrast-induced AKI not requiring dialysis (23). In patients undergoing primary PCI for myocardial infarction (MI), short- and long-term mortality rates were also significantly higher in those who developed contrast-induced AKI (24,25). Furthermore, in this group, it has been shown that contrast-induced AKI is an independent predictor of mortality (26).

Impact of contrast-induced AKI on clinical course and outcome. As well as an increased risk of death, contrast-induced AKI is also associated with other adverse outcomes including late cardiovascular events after PCI. In 1 registry of 5,967 PCI patients, the development of contrast-induced AKI was associated with an increased incidence of MI and target vessel revascularization at 1 year (26). Another large PCI study documented the link between contrast-induced AKI, post-procedural increases in creatine kinase-myocardial band (CK-MB) subfraction, and the risk of late cardiovascular events (27). In a group of 5,397 patients, a post-procedural rise in SCr was a more powerful predictor of late mortality than CK-MB. Creatinine increases were associated with a 16% rate of death or MI at 1 year, rising to 26.3% when CK-MB levels were also elevated after the procedure (27).

More in-hospital events such as bypass surgery, bleeding requiring transfusion, and vascular complications were observed in patients who developed contrast-induced AKI, both in those with previous renal dysfunction and those with previously normal renal function. At 1 year, the cumulative rate of major adverse cardiac events was significantly higher in patients who had developed contrast-induced AKI ($p < 0.0001$ for patients with and without chronic kidney disease [CKD]) (28). However, others have observed no difference in the rates of MI and target vessel revascularization in patients with contrast-induced AKI (23).

The development of contrast-induced AKI has also been associated with an increased hospital stay. In 1 series, the post-procedure hospital stay was longer for patients who developed contrast-induced AKI, regardless of baseline renal function (28). In a series of 200 patients undergoing PCI for acute MI, patients who developed contrast-induced AKI had a longer hospital stay, a more complicated clinical course, and a significantly increased risk of death compared with those without contrast-induced AKI (25).

Economic impact. A recent economic analysis of the direct costs associated with contrast-induced AKI showed that the average additional cost was $10,345 for the hospital stay and $11,812 to 1 year (29). The incidence and outcome data were determined from studies identified through a systematic literature search and combined with unit costs from the literature in a decision analytic model. The major driver of

Table 1 Consensus Statements

Consensus Statement 1
Contrast-induced AKI is a common and potentially serious complication after the administration of contrast media in patients at risk for acute renal injury.
Consensus Statement 2
The risk of contrast-induced AKI is elevated and of clinical importance in patients with chronic kidney disease (particularly when diabetes is also present), recognized by an eGFR rate <60 ml/min/1.73 m^2.
Consensus Statement 3
When serum creatinine or eGFR is unavailable, then a survey may be used to identify patients at higher risk for contrast-induced AKI than the general population.
Consensus Statement 4
In the setting of emergency procedures, where the benefit of very early imaging outweighs the risk of waiting, the procedure can be performed without knowledge of serum creatinine or eGFR.
Consensus Statement 5
The presence of multiple contrast-induced AKI risk factors in the same patient or high-risk clinical scenarios can create a very high risk (~50%) for contrast-induced AKI and (~15%) acute renal failure requiring dialysis after contrast exposure.
Consensus Statement 6
In patients at increased risk for contrast-induced AKI undergoing intra-arterial administration of contrast, ionic high-osmolality agents pose a greater risk for contrast-induced AKI than low-osmolality agents. Current evidence suggests that for intra-arterial administration in high-risk patients with chronic kidney disease, particularly those with diabetes mellitus, nonionic, iso-osmolar contrast is associated with the lowest risk of contrast-induced AKI.
Consensus Statement 7
Higher contrast volumes (>100 ml) are associated with higher rates of contrast-induced AKI in patients at risk. However, even small (~30 ml) volumes of iodinated contrast in very high-risk patients can cause contrast-induced AKI and acute renal failure requiring dialysis, suggesting the absence of a threshold effect.
Consensus Statement 8
Intra-arterial administration of iodinated contrast appears to pose a greater risk of contrast-induced AKI above that with intravenous administration.
Consensus Statement 9
Adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 ml/kg/h) for 3–12 h before the procedure and continued for 6–24 h afterwards can lessen the probability of contrast-induced AKI in patients at risk. The data on oral as opposed to intravenous volume expansion as a contrast-induced AKI prevention measure are insufficient.
Consensus Statement 10
No adjunctive medical or mechanical treatment has been proven to be efficacious reducing the risk of AKI after exposure to iodinated contrast. Prophylactic hemodialysis or hemofiltration has not been validated as an effective strategy.

AKI = acute kidney injury; eGFR = estimated glomerular filtration.
Adapted from McCullough et al. (13).

the increased costs associated with contrast-induced AKI was the cost of the longer initial hospital stay.

Risk of contrast-induced AKI requiring dialysis. While most cases of contrast-induced AKI reflect mild transient impairment of renal function, dialysis is needed in a small proportion of patients. The need for dialysis after contrast-induced AKI varies according to patients' underlying risks at the time of contrast administration but is generally less than 1% (17,30,31), although it was considerably higher in some older studies with high-osmolal contrast media (HOCM) (32,33). In contemporary studies, contrast-induced AKI requiring dialysis developed in almost 4% of patients with underlying renal impairment (34) and 3% of patients undergoing primary PCI for acute coronary syndromes (25). Although contrast-induced AKI requiring dialysis is relatively rare, the impact on patient prognosis is considerable, with high hospital and 1-year mortality rates (17,23).

Pathophysiology of Contrast-Induced AKI

Chronic kidney disease is both necessary and sufficient for the development of contrast-induced AKI. In patients with CKD, identified by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (which roughly corresponds in the elderly to a SCr >1.0 mg/dl in a woman and >1.3 mg/dl in a man), there is a considerable loss of nephron units, and the residual renal function is vulnerable to declines with renal insults (iodinated contrast, cardiopulmonary bypass, renal-toxic medications, and so on). Thus, the pathophysiology of contrast-induced AKI assumes baseline reduced nephron number, with superimposed acute vasoconstriction caused by the release of adenosine, endothelin, and other renal vasoconstrictors triggered by iodinated contrast. After a very brief increase in renal blood flow, via the above mechanisms, there is an overall ~50% sustained reduction in renal blood flow lasting for several hours (Fig. 1). There is concentration of iodinated contrast in the renal tubules and collecting ducts, resulting in a persistent nephrogram on fluoroscopy. This stasis of contrast in the kidney allows for direct cellular injury and death to renal tubular cells. The degree of cytotoxicity to renal tubular cells is directly related to the length of exposure those cells have to iodinated contrast, hence, the importance of high urinary flow rates before, during, and after contrast procedures. The sustained reduction in renal blood flow to the outer medulla leads to medullary hypoxia, ischemic injury, and death of renal tubular cells. By these 2 mechanisms, it is believed that other organ injury processes including oxidative stress and inflammation may play a further role. Any superimposed insult such as sustained hypotension in the catheterization laboratory, microshowers of atheroembolic material from

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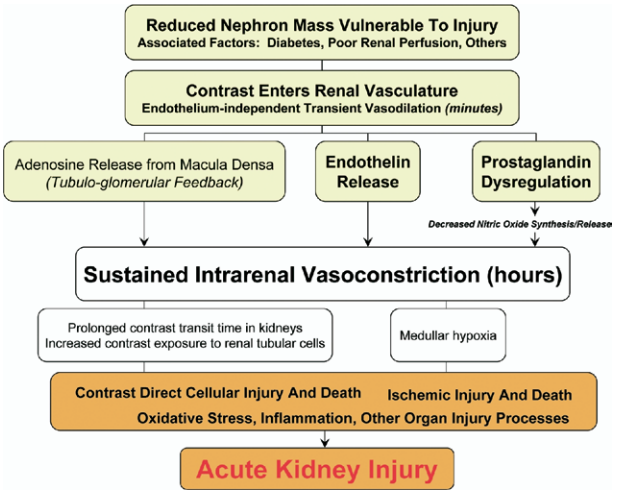

Figure 1 **Postulated Pathophysiology of Contrast-Induced AKI**

In the presence of a reduced nephron mass, the remaining nephrons are vulnerable to injury. Iodinated contrast, after causing a brief (minutes) period of vasodilation, causes sustained (hours to days) intrarenal vasoconstriction and ischemic injury. The ischemic injury sets off a cascade of events largely driven by oxidative injury causing death of renal tubular cells. If a sufficient mass of nephron units are affected, then a recognizable rise in serum creatinine will occur.

catheter exchanges or the use of intra-aortic balloon counterpulsation, or a bleeding complication can amplify the injury processes occurring in the kidney. A detailed review of pathophysiology is outside the scope of this report, and the reader is referred to a published review for further information (9).

The Role of Baseline Renal Function Screening

Virtually every report describing risk factors for contrast-induced AKI lists abnormal baseline SCr, low GFR, or CKD as risk factors. Almost every multivariate analysis has shown that CKD is an independent risk predictor for contrast-induced AKI (1,15,22,30,34,35). The risk of contrast-induced AKI is increased in patients with an eGFR <60 ml/min/1.73 m^2 (stage 3 to 5 CKD), and special precautions should be taken in these patients. These statements apply to stable renal function. In critically ill patients, renal function may be dynamic and compromised (due to cardiogenic shock, heart failure, drug-induced injury, and so on), making the risk state greater, and thus, clinical judgement must be applied to the assessment of baseline renal function.

Measurement of baseline renal function. It is important to assess renal function before administration of contrast medium to ensure that appropriate steps are taken to reduce the risk. Since SCr alone does not provide a reliable measure of renal function, the National Kidney Foundation Kidney Disease Outcome Quality Initiative recommends that clinicians should use an eGFR calculated from the SCr as an index of renal function rather than using SCr (36) in stable patients.

Use of surveys/questionnaires. It is highly desirable to have an eGFR value available in order to assess the risk of contrast-induced AKI, but this may be impractical in some circumstances, especially in outpatient cardiac computed tomography angiography. Where renal function data are unavailable, a simple survey or questionnaire may be used to identify outpatients at higher risk for AKI in whom appropriate precautions should be taken (37–39). A brief 7-item survey inquires on the following: 1) history of renal disease; 2) prior renal surgery; 3) proteinuria; 4) diabetes mellitus (DM); 5) hypertension; 6) gout; and 7) use of nephrotoxic drugs (nonsteroidal anti-inflammatory agents, and so on). The majority of patients with CKD would have 1 or more positive responses to these questions. For patients undergoing scheduled catheterization procedures, the SCr should be available before contrast is given.

Emergency situations. In the setting of emergency procedures, where the benefit of very early imaging outweighs the risk of waiting for the results of a blood test, it may be necessary to proceed without SCr assessment or GFR estimation (8). This is particularly relevant to patients undergoing emergency catheterization or primary PCI. It is suggested that a baseline blood sample is taken before the emergency procedure to enable monitoring afterwards even if the initial result is not immediately known. However, when possible, an indication should be obtained of the likelihood that the patient has impaired renal function that may increase the risk of AKI, to enable suitable precautions to be taken.

Risk Markers for AKI After Iodinated Contrast

The term "risk marker" as opposed to "risk factor" is preferred since many of the indicators of risk for contrast-induced AKI are nonmodifiable and are not necessarily causative (6). Baseline renal filtration function is a surrogate for reduced nephron mass and renal parenchymal function (9). As indicated in the preceding text, because CKD implies a loss of nephron units, the risk of contrast-induced AKI is increased in patients with an eGFR <60 ml/min/1.73 m^2, and special precautions should be taken in these patients (9).

Other risk markers include DM (26,28), volume depletion (40), nephrotoxic drugs, hemodynamic instability (27,41), and other comorbidities. Importantly, DM is neither necessary nor sufficient as a determinant for contrast-induced AKI. However, DM appears to act as a risk multiplier, meaning that in a patient with CKD it amplifies the risk of contrast-induced AKI (Fig. 2). Several large series of PCI patients have shown an association between contrast-induced AKI and indicators of hemodynamic instability such as periprocedural hypotension and use of an intra-aortic balloon pump (26,28). It is not surprising that hypotension increases the risk of contrast-induced AKI

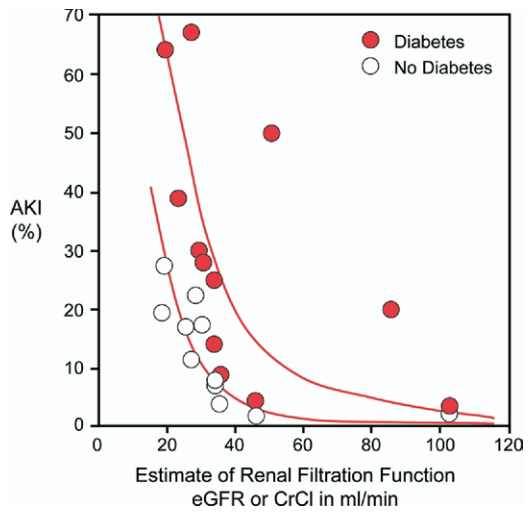

Figure 2 **Risk of Contrast-Induced AKI According to Baseline Renal Function (eGFR or CrCl ml/min)**

Contrast-induced acute kidney injury (AKI) was defined as serum creatinine increase of 25% and/or 0.5 mg/dl and is shown separately for patients with **(solid circles)** and without **(open circles)** diabetes. CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate. Data adapted from McCullough et al. (12).

since it increases the likelihood of renal ischemia and is a significant risk factor for acute renal failure in acutely ill patients. Anemia has also been reported as a predictor of contrast-induced AKI (42).

The effect of risk factors is additive, and the likelihood of contrast-induced AKI rises sharply as the number of risk factors increases (17,41). A similar pattern of additive risk has been documented for AKI requiring dialysis (30).

The additive nature of risk has allowed the development of prognostic scoring schemes (15,41), but since none of the published schemes has been adequately studied or prospectively validated in different populations, it is not appropriate to recommend routine use of any particular risk scoring in clinical practice. However, the concept is that in a patient with CKD, DM, and other comorbidities, predicted risks of contrast-induced AKI and emergency dialysis can approach ~50% and ~15%, respectively.

High-Risk Situations and Procedures

Many clinical situations may arise in which the risk of contrast-induced AKI is increased, with the most common scenario in the catheterization laboratory being cardiogenic shock (6). While in general, the benefits of revascularization outweigh the risks of the procedure, in the setting of shock requiring the placement of an intra-aortic balloon pump, considerably higher rates of contrast-induced AKI can be expected. A common scenario in complicated patients is repeated exposure to iodinated contrast over a period of a few days. While there are no studies on the ideal interim "rest" period for the kidneys, the general principal is that if additional contrast is given in the setting of AKI, outcomes are likely to worsen. Most clinical trials have used an interim period of 10 days from a prior procedure to be sure the patient has not incurred AKI from the first procedure. Because of the added insult of cardiopulmonary bypass, the risk of contrast-induced AKI in patients undergoing emergency coronary artery bypass surgery after angiography is increased. Finally, the published literature on the risk of contrast-induced AKI in heart or renal transplant recipients is inconsistent, and clinicians should be conservative and consider them at high risk (6).

Contrast Medium Use

Choice of contrast medium. Iodinated contrast media packages iodine atoms, which are radiopaque, on carbon-based molecules, which are water soluble. Contrast media is classified according to osmolality, which reflects the total particle concentration of the solution (the number of molecules dissolved in a specific volume). Contrast media can be categorized according to osmolality (HOCM ~2,000 mOsm/kg, low-osmolal [LOCM] 600 to 800 mOsm/kg, and isosmolal [IOCM] 290 mOsm/kg) (7). Over the past 40 years, the osmolalities of available contrast media have been gradually decreased to physiological levels. In the 1950s, only HOCM (e.g., diatrizoate) with osmolality 5 to 8 times that of plasma were used. In the 1980s, LOCM agents such as iohexol, iopamidol, and ioxaglate were introduced, having osmolality 2 to 3 times greater than that of plasma. In the 1990s, iso-osmolar nonionic iodixanol with the same physiological osmolality as blood was developed. Red blood cell deformation, systemic vasodilation, intrarenal vasoconstriction, as well as direct renal tubular toxicity are all more common in contrast agents with osmolality greater than that of blood. In a meta-analysis of studies before 1992, the pooled odds ratio for the incidence of contrast-induced AKI events (rise in SCr of >0.5 mg/dl in 25 trials was 0.61), 95% confidence interval 0.48 to 0.77, indicating a significant reduction in risk with LOCM compared with that seen with HOCM (43). Studies published since this meta-analysis generally support these findings (44). Most studies comparing different LOCM agents have been small trials that have not shown clinically relevant variation within this class (7).

Iodixanol has been shown to have the lowest risk for contrast-induced AKI in patients with CKD and DM (45,46). In a pooled analysis of 16 head-to-head, randomized trials (2,727 patients) of intra-arterial contrast medium, the incidence of contrast-induced AKI was significantly lower with iodixanol than with LOCM (Fig. 3) (47). A systematic review by Solomon (48) also demonstrated the lowest risk of contrast-induced AKI with iodixanol. This study included a total of 17 prospective clinical trials (1,365 patients), but only 2 of these trials were randomized head-to-head comparisons of iodixanol versus LOCM, and the other data came from the placebo arms of 13 trials of

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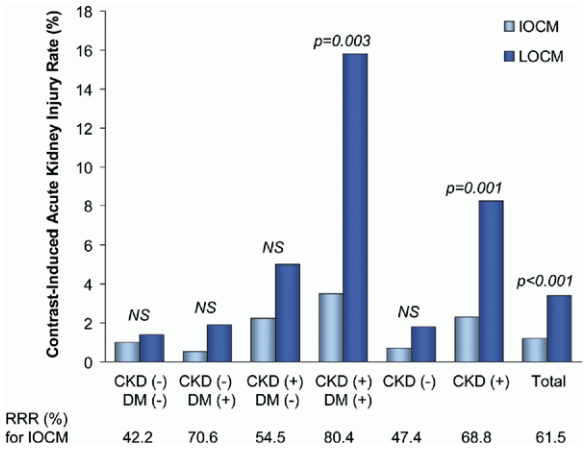

Figure 3 **Rates of Contrast-Induced AKI in a Meta-Analysis of 16 Trials of Iso-Osmolar Iodixanol**

Relative risk reductions (RRRs) are for iso-osmolar (IOCM) compared with low-osmolar contrast media (LOCM). CKD = baseline chronic kidney disease defined as an estimated creatinine clearance <60 ml/min; DM = diabetes mellitus. Data adapted from McCullough et al. (47).

preventive strategies for contrast-induced AKI and the LOCM arms of 2 trials comparing LOCM and HOCM. Finally, a meta-analysis of the renal tolerability of another IOCM, iotrolan 280 (not approved for intravascular use), provides further evidence that IOCM are associated with a lower risk of contrast-induced AKI (49). In this analysis of 14 double-blind studies, it was found that iotrolan had less effect on renal function that the LOCM with which it was compared (iopamidol, iohexol, iopromide).

Several more clinical trials have been published since the literature search undertaken by the CIN Consensus Working Panel supporting the view that iodixanol is the least nephrotoxic agent available for intravascular use. A Korean head-to-head randomized trial showed a significantly lower rate of contrast-induced AKI with iodixanol compared with LOCM in high-risk patients undergoing coronary angiography (50). However, in recent trials of lower-risk patients undergoing computed tomography, the rates of contrast-induced AKI were similar with iodixanol and LOCM after intravenous administration for computed tomography (51) or intracoronary administration (52). In both trials, the diagnosis of contrast-induced AKI depended on a single nonstandardized SCr measurement after the procedure, yielding low event rates in insufficient power to find differences between the agents.

Finally, the American College of Cardiology/American Heart Association guidelines for the management of acute coronary syndromes patients with CKD listed the use of IOCM as a class I, Level of Evidence: A recommendation (53). The National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines have also recommended use of IOCM in renal dialysis patients to minimize the chances of volume overload and complications before the next dialysis session (7).

Volume of contrast. Numerous studies have shown that the volume of contrast medium is a risk factor for contrast-induced AKI. The mean contrast volume is higher in patients with contrast-induced AKI, and most multivariate analyses have shown that contrast volume is an independent predictor of contrast-induced AKI (17,26,30,41). However, even small volumes (~30 ml) of contrast medium can have adverse effects on renal function in patients at particularly high risk (54). As a general rule, the volume of contrast received should not exceed twice the baseline level of eGFR in milliliters (55). This means for patients with significant CKD, a diagnostic catheterization should plan to use <30 ml of contrast, and if followed by PCI then <100 ml should be a reasonable goal.

Intra-arterial versus intravenous administration. A number of studies have provided circumstantial evidence that the risk of contrast-induced AKI may be higher after intra-arterial than after intravenous injection (56,57). However, none of these studies provides an insight into the significance of the route of administration for contrast-induced AKI risk in contemporary practice, especially with regard to computed tomography studies, when a comparatively large volume of contrast medium may be given as a compact intravenous bolus rather than an infusion. Current practice of cardiac computed tomography angiography calls for contrast loads of 80 to 120 ml. At these levels, in a high-risk patient for contrast-induced AKI, a single procedure with diagnostic catheterization and PCI if warranted with operator-controlled minimization of contrast exposure appears to be a more reasonable strategy than cardiac computed tomography angiography followed by angiography.

Other Strategies for Reducing Risk

Withholding nephrotoxic drugs. While there are no withdrawal studies in this area, it is reasonable practice to hold nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, high-dose loop diuretics, aminoglycosides, and other nephrotoxic agents if possible for several days before contrast exposure. It is routine practice to hold metformin before all contrast procedures not because metformin itself is nephrotoxic, but because in the setting of AKI if metformin is continued, lactic acidosis can develop leading to systemic complications and death. In the setting of accidental administration of metformin in a patient with AKI, the metformin can be cleared from the body with dialysis. As a general rule, metformin should not be restarted until the clinician is confident that the patient has not incurred AKI. Finally, there is controversy over whether drugs that block the renin angiotensin system should be held or continued for contrast procedures. Clinical trials of these agents to prevent contrast-induced AKI have not demonstrated harm, with 1 larger trial of an angiotensin-II receptor blocker yet to report, so at the time of this writing it is reasonable to

continue these drugs for their chronic cardiovascular and renal indications.

Volume expansion. Volume expansion and treatment of dehydration has a well-established role in prevention of contrast-induced AKI, although few studies address this theme directly. There are limited data on the most appropriate choice of intravenous fluid, but the evidence indicates that isotonic crystalloid (saline or bicarbonate solution) is probably more effective than half-normal saline (58). Additional confirmatory trials with sodium bicarbonate (59) are needed because the largest trial to date showed no benefit of sodium bicarbonate over normal saline (60).

There is also no clear evidence to guide the choice of the optimal rate and duration of infusion. However, good urine output (>150 ml/h) in the 6 h after the procedure has been associated with reduced rates of AKI in 1 study (61). Since not all of intravenously administered isotonic crystalloid remains in the vascular space, in order to achieve a urine flow rate of at least 150 ml/h, ≥1.0 to 1.5 ml/kg/min of intravenous fluid has to be administered for 3 to 12 h before and 6 to 12 h after contrast exposure. Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion (62).

Dialysis and hemofiltration. Contrast medium is removed by dialysis, but there is no clinical evidence that prophylactic dialysis reduces the risk of AKI, even when carried out within 1 h or simultaneously with contrast administration. Hemofiltration, however, performed 6 h before and 12 to 18 h after contrast deserves consideration given reports of reduced mortality and need for hemodialysis in the post-procedure period in very high-risk patients (SCr 3.0 to 4.0 mg/dl, eGFR 15 to 20 ml/min/1.73 m^2) (63,64). Hemofiltration works to ensure adequate intravascular volume, reduces uremic toxins that may worsen AKI, and provides stability to the high-risk patient after the procedure, reducing the risks of oliguria, volume overload, and electrolyte imbalance, which are associated with short-term mortality. Under the direction of a nephrologist, a double lumen catheter is placed in a jugular or femoral vein for blood withdrawal and reinfusion and connected with an extracorporeal circuit. Blood is driven through the circuit by means of a peristaltic pump (e.g., Prisma hemofiltration pump, Gambro, Inc., Lakewood, Colorado) at a rate of 100 ml/min. Isotonic replacement fluid (post-dilution hemofiltration) is set at a rate of 1,000 ml/h and is matched with the rate of ultrafiltrate production so that no net fluid loss occurs. The cardiologist should be aware that hemofiltration calls for a 5,000-IU heparin bolus before initiation followed by a continuous heparin infusion of 500 to 1,000 IU/h through the inflow side of the catheter. At the time of the cardiac procedure, the hemofiltration treatment should be stopped, and the circuit temporarily filled with a saline solution and short circuited to exclude the patient without interruption of the flow. Immediately after the procedure, the hemofiltration should be restarted. This approach should be considered only in the very highest-risk patient in conjunction with nephrology consultation and dialysis planning.

Pharmacologic strategies. There are currently no approved pharmacologic agents for the prevention of AKI. With iodinated contrast, the pharmacologic agents tested in small trials that deserve further evaluation include the antioxidants ascorbic acid and N-acetylcysteine (NAC), statins, aminophylline/theophylline, and prostaglandin E_1 (10).

Of these agents, only ascorbic acid has been tested in a multicenter, blinded, placebo-controlled trial (n = 231) and been shown to reduce rates of contrast-induced AKI. The dose of ascorbic acid (vitamin C over the counter) used in this trial was 3 g orally the night before and 2 g orally twice a day after the procedure (65).

Although popular, NAC has not been consistently shown to be effective. Nine published meta-analyses have been published (10), all documenting the significant heterogeneity between studies and pooled odds ratios for NAC approaching unity. Importantly, only in those trials where NAC reduced SCr below baseline values because of decreased skeletal muscle production did renal injury rates appear to be reduced. Thus, NAC appears to falsely lower Cr and not fundamentally protect against AKI. However, NAC as an antioxidant has been shown to lower rates of AKI and mortality after primary PCI in 1 trial (66). The recently published REMEDIAL (Renal Insufficiency Following Contrast Media Administration) trial suggested that the use of volume supplementation with sodium bicarbonate together with NAC was more effective than NAC alone in reducing the risk of AKI (67). Dosing of NAC has varied in the trials; however, the most successful approach has been with 1,200 mg orally twice a day on the day before and after the procedure.

Fenoldopam, dopamine, calcium-channel blockers, atrial natriuretic peptide, and L-arginine have not been shown to be effective in the prevention of contrast-induced AKI. Furosemide, mannitol, and an endothelin receptor antagonist are potentially detrimental (10).

In general, cardiovascular patients undergoing procedures with iodinated contrast have either high risk for atherosclerosis or have the anatomic presence of disease. Therefore, the vast majority of patients should be on statin therapy with a common low-density lipoprotein cholesterol target of <70 mg/dl. Several studies have demonstrated that patients continued on statins during cardiovascular procedures including PCI and coronary artery bypass grafting have lower rates of AKI (68). All small randomized trials published to date support this concept as well (69,70). Preservation of endothelial function at the level of the glomerulus and reductions in systemic inflammatory factors are postulated mechanisms by which statins may have renoprotective effects. Thus, statins should be a standard of care for patients undergoing these procedures for a variety of reasons, and should be started at baseline and continued over

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the long-term course of care provided they are well tolerated (without skeletal muscle or liver adverse effects).

An integrated advanced algorithm for the management of contrast-induced AKI is presented in Figure 4. It should be noted that there are no approved pharmaceutical agents for the prevention of this complication; thus, the practitioner should be cautious with the use of any of the drugs suggested. Importantly, all patients at risk for contrast-induced AKI should have follow-up Cr and electrolyte monitoring daily while in hospital, and then at 48 to 96 h after discharge. Rehospitalization is reasonable for uremic symptoms, hyperkalemia, and volume overload in the setting of AKI.

Novel Biomarkers

As discussed in the preceding text, SCr is both an indirect and insensitive marker of baseline kidney function and of AKI. Thus, there is considerable interest in developing blood and urine biomarkers for AKI analogous to troponin for acute MI. Neutrophil gelatinase-associated lipocalin, a member of the lipocalin family, is readily excreted and detected in urine, due to its small molecular size (25 kDa) and resistance to degradation. Neutrophil gelatinase-associated lipocalin is highly accumulated in the human kidney cortical tubules, blood, and urine after nephrotoxic and ischemic injuries such as exposure to iodinated contrast. Thus, whole blood neutrophil gelatinase-associated lipocalin might represent an early, sensitive biomarker for AKI being developed for point-of-care use in the catheterization laboratory (71,72). Finally, Cystatin C is a serum protein that is filtered out of the blood by the kidneys and that serves as a measure of kidney function. Cystatin C is produced steadily by all types of nucleated cells in the body. Its low molecular mass allows it to be freely filtered by the glomerular membrane in the kidney. Its concentration in blood correlates with the glomerular filtration rate. The levels of Cystatin C are independent of weight and height, muscle mass, age, and gender. Measurements can be made and interpreted from a single random sample. Cystatin C is a better marker of the glomerular filtration rate and kidney function than Cr and is cleared for use by the U.S. Food and Drug Administration. It is expected that this marker will replace SCr in the future as the blood marker of renal filtration function.

Future Preventive Approaches

Because contrast-induced AKI has a timed injury to the kidney, it is one of the most amenable forms of AKI for clinical trials. Future approaches include large planned studies of oral and intravenous antioxidants (including a potent oral antioxidant, deferiprone), intrarenal infusions of renal vasodilators using flow directed catheters, forced hydration with marked elevations of urine output to reduce the transit time of iodinated contrast in the renal tubules, systemic cooling, and novel, hopefully less toxic, forms of radio-opaque contrast agents. Another novel approach may involve coronary sinus withdrawal of blood and contrast after intracoronary injection, thus reducing the volume of contrast delivered downstream to the kidneys (73,74). If

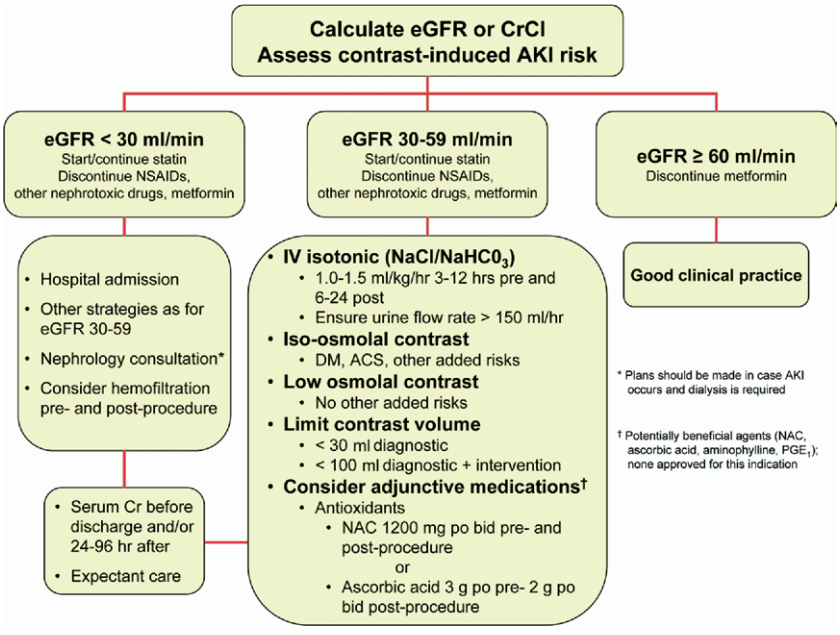

Figure 4 Advanced Algorithm for Management of Patients Receiving Iodinated Contrast Media

ACS = acute coronary syndromes; bid = twice daily; Cr = creatinine; DM = diabetes mellitus; IV = intravenous; NAC = N-acetylcysteine; NSAIDs = nonsteroidal anti-inflammatory drugs; PGE_1 = prostaglandin E_1; po = by mouth; other abbreviations as in Figure 2.

cardiovascular procedures could be performed with no risk of AKI, it is expected that major adverse cardiac and medical complications could be appreciably reduced. This is exactly the hypothesis encouraged in future, large-scale outcomes trials of contrast-induced AKI prevention.

Conclusions

The consensus statements summarized in this chapter can help guide the management of patients receiving iodinated contrast medium in the cardiac and vascular imaging laboratory. Multicenter, large-scale randomized trials of preventive strategies are needed to evaluate changes in renal function and meaningful clinical outcomes. Future, nontoxic imaging agents are needed to manage the ever-increasing numbers of vulnerable patients undergoing cardiac procedures.

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