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EDITORIAL COMMENT

Risk Reduction of Acute Kidney Injury From Iodinated Contrast

Is True Prevention a Search for the Holy Grail?*

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Contrast-induced nephropathy (CIN) was recognized early on as a potential risk in patients undergoing diagnostic imaging with iodinated contrast. Initial definitions varied, pathophysiology was poorly understood, and risk factors were unclear. This led to more than 2 decades of studies that expanded the science of CIN. At-risk patients were identified, calculations for risk created, and techniques for risk reduction proposed (1). The name of CIN evolved to represent the complexity of this process, whereby at-risk patients, imaged either invasively or noninvasively with contrast, developed contrast-induced acute kidney injury (CI-AKI). Extensive efforts have focused on avoiding injury despite an increasingly high-risk patient population. However, as is the case with the AVERT trial, finding a cure for the prevention of CK-AKI has remained elusive (2).

With contrast volume reduction a tenet for CI-AKI risk reduction, the AVERT trial randomized at risk patients for CI-AKI to receive a contrast modulator designed to minimize volume. Patients undergoing coronary angiography with and without percutaneous coronary intervention (PCI) were included, and the study was powered to identify risk reduction. The demographic data supported similarities between the groups, and adequate hydration was ensured. The AVERT system was safe and successful in both contrast volume reduction and acceptable image quality. However, in this issue of *JACC: Cardiovascular Interventions,* the study by Mehran et al. (2) states that there was no difference seen in CI-AKI between the groups, with each having an incidence of approximately 27%, in this high-risk population. Future trials designed specifically for a patient population requiring higher contrast volume, such as complex PCI, may be more reflective of potential risk reduction.

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The AVERT trial is another example of a well-conceived study to address CI-AKI prevention. These trials now benefit from a uniform CI-AKI definition, which has provided a better understanding of the epidemiology. The Kidney Disease Improving Global Outcomes working group defined CI-AKI as an increase in serum creatinine of ≥0.3 mg/dl (≥26.5 μmol/l), within 48 h post-contrast (3). Given a standard definition, the incidence of CI-AKI can be more accurately estimated; for PCI, it is approximately 7% (4). The clinical course of CI-AKI is understood, with creatinine peak at 48 to 72 h returning to baseline by 1 to 2 weeks; permanent injury requiring hemodialysis is rare, at 0.3% (4). Prognostically, patients who develop CI-AKI, often a marker of systemic disease severity, have consistently higher rates of virtually every PCI complication (1).

A disease-specific treatment for CI-AKI would benefit from a specific pathology, which is lacking. Direct cytotoxic effects to the renal tubules has been proposed, with concomitant ischemic injury to the renal medulla secondary to the osmolality of contrast, vasoconstriction, or decreased vasodilation related to oxidative stress (5). Risk factors have been identified, with chronic kidney disease, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2, the most powerful and often related to the severity of

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TABLE 1 RENALL: A Contrast-Induced Acute Kidney Injury Risk Reduction Acronym

R	Risk assessment with pre-procedural planning; no left ventriculography; manage contrast from beginning of the case; stage PCI, if possible, to delay contrast re-exposure 48–72 h
E	eGFR: know baseline renal function of all patients; treat patients with eGFR <60 ml/min/1.73 m^2 as high risk; special attention for very high risk (eGFR <30 ml/min/1.37 m^2), with nephrology involvement as appropriate
N	Normal saline: pre- and post-hydration with isotonic crystalloid solutions
A	Avoid nephrotoxic drugs, dehydration, and prior contrast exposure
L/L	Low-osmolar/iso-osmolar contrast: long-term follow-up with post-procedural Cr check, preferably at 48–72 h

Cr = creatinine; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

renal disease (1). Other risk factors include presentation (acute coronary syndrome, heart failure, and cardiogenic shock), arterial injection, certain drugs, anemia, age, and contrast volume. Risk models have been developed to predict CI-AKI (6,7). Contrast volume predicts CI-AKI risk with a volume-to-creatinine clearance ratio of >3.7 a predictor of creatinine increase (8). A maximal contrast dose, defined as 5 ml × body weight (kg)/serum creatinine (mg/dl), may predict the risk for CI-AKI requiring hemodialysis (9).

Because treatment options are limited once CI-AKI occurs, it is key to have risk reduction protocols in place and overseen by the quality committee. Publications have outlined these recommendations with specific suggestions provided on the basis of baseline renal function (1,10). **Table 1** provides an acronym for this discussion. High-risk patients must be identified and adequate hydration ensured. Although oral hydration regimens may be inadequate, avoiding dehydration requires reassessment of prolonged pre-procedural intake restrictions (nil per os). The CI-AKI Consensus Working Panel recommendation for intravenous therapy is an isotonic crystalloid (1.0 to 1.5 ml/kg/h) for 3 to 12 h pre-procedure and for 6 to 24 h post-procedure; caution is required in patients with heart failure (11). Limiting contrast dose requires both pre-case planning and continuous dose awareness during the case. Minimizing test doses, smaller catheters, careful shot selection, avoiding ventriculography, and biplane angiography are all recommended. If clinically appropriate, ad hoc PCI should be deferred, with the patient returning in 48 to 72 h. This allows the recognition of CI-AKI and may then again be deferred until renal function recovers. Nephrology involvement with pre-procedural planning or post-care issues may be beneficial.

As with the AVERT contrast modulator, significant effort has taken place to further develop risk reduction techniques, often without benefit. Although a complete review is beyond the scope of this editorial, these are some additional examples. Low-osmolar iodinated compounds were shown to reduce CI-AKI. However, despite theoretically more advantageous, iso-osmolar contrast has not consistently reduced the rates of CI-AKI (12). *N*-acetylcysteine, an antioxidant, and isotonic sodium bicarbonate, urine alkalization, were proposed with conflicting results. The PRESERVE trial randomly assigned more than 5,000 high-risk patients for CI-AKI to study these agents. No difference was seen in the 90-day occurrence of neither major adverse events nor significant difference in the rate of CI-AKI (13). High-dose statins show promise, though early meta-analyses questioned their benefits in chronic kidney disease (14). As I review these studies, I recall my Vermont professor saying, "You can't make a silk purse out of a sow's ear." End-stage renal disease is end stage; critically ill patients are critically ill. No contrast dose is entirely safe in high-risk patients with other acute kidney injury etiologies, including dehydration, drug toxicities, hemodynamic instability, and atheroembolic or cholesterol-embolic disease (15).

Interventional cardiology has seen advances in both technology and operator skill such that previously inoperable patients can now be treated. Quality initiatives have similarly expanded to identify risk and track outcomes. CI-AKI has exemplified this by identifying patients at risk for renal injury and then instituting techniques to decrease risk. However, the competing curves of increased risk from patient acuity and technical advances for risk reduction will not likely eliminate risk. Although the ardent researcher continues to seek a cure, the clinician must embrace the essentials of CI-AKI risk reduction with pre- and post-hydration and contrast dose reduction from procedure onset. These best practices must be instituted as we seek the potential CI-AKI holy grail for prevention, relying on dedicated investigators, as in AVERT, to continue this quest.

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