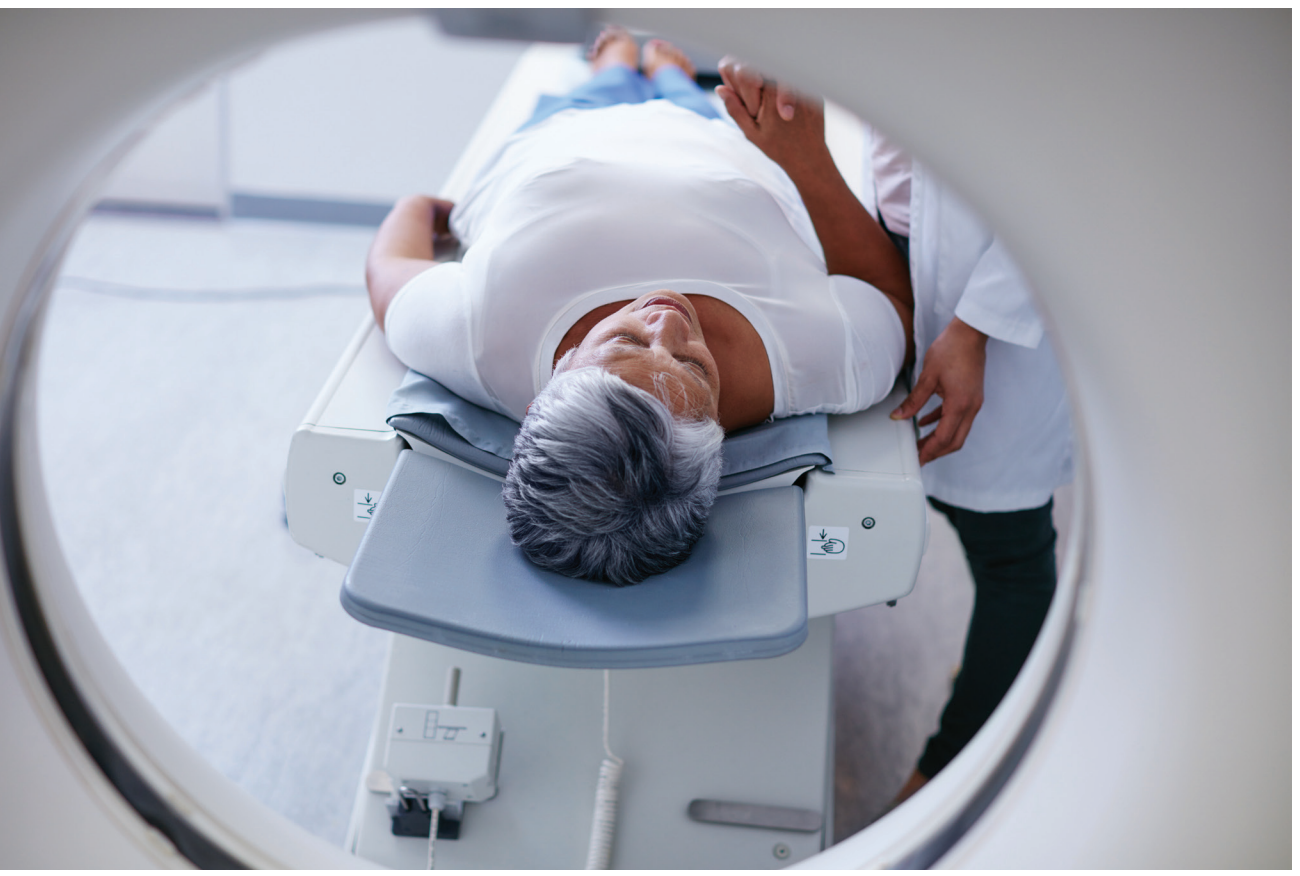
The Death of Contrast-Induced Nephropathy Is Premature

By Michael R. Rudnick, MD, and Amanda Leonberg-Yoo, MD

The occurrence of acute kidney injury (AKI) resulting from the intravascular administration of contrast media (CM), commonly referred to as contrast-induced nephropathy (CIN), has become firmly entrenched.

CIN has been described with both intra-arterial and intravenous (IV) administration of CM. Most clinical studies of CIN occur in a population receiving CM during coronary angiography, even though most intravascular CM exposures occur via IV administration during contrast-enhanced computed tomography (CECT).



Within the past decade, an increasing number of studies have called into question the true incidence and even the existence of CIN after IV CM administration. This has led some physicians to opine that CIN after IV CM administration has been overstated, may not even occur, and is not of a sufficient magnitude to be clinically significant (1). Physicians should be concerned about the implications of these opinions, given the associations of AKI with short-term and long-term mortality and the development of chronic kidney disease (CKD) (2, 3). Thus, in order to "first do no harm," it is important to critically examine the literature reports that have been purported to negate the risk of CIN from IV CM administration.

The initial studies of CIN after CECT were limited by the absence of control groups of patients who underwent unenhanced computed tomography (CT). The inclusion of a control group is necessary to determine whether factors other than CM may be responsible for the observed AKI in a given study. The next generation of studies included a control group and demonstrated similar rates of AKI after CECT and unenhanced CT, with conclusions that the entity of CIN after IV CM either had been overstated or does not exist (1). These studies have several limitations, including small sample sizes (especially of high-risk patients) and evidence of selection bias. Selection bias could steer patients with predisposition to AKI other than CM exposure to receive unenhanced CT imaging, whereas AKI in the CECT group could still be attributable to CM exposure, thus biasing the risk of CIN toward the null in these studies (1). Thus, the similar incidence of AKI could be attributable to factors other than CM that may have influenced inclusion in the control group. In an effort to diminish the impact of selection bias, contemporary studies were performed with the use of propensity score methods. Propensity scores adjust for risk factors that may influence receipt of the exposure variable (CECT in this case) in an attempt to make retrospective observational analyses more similar to prospective randomized trials.

It is instructive to review two large propensity score–adjusted studies on IV CIN. McDonald et al. (4) performed a retrospective propensity score–adjusted analysis of 12,508 patients to evaluate the risk of AKI in a cohort exposed to CECT or unenhanced CT. Patients in both groups were stratified by baseline estimated GFR (eGFR) and were matched 1:1 by propensity score. The incidences of AKI between CECT and unenhanced CT were similar for each eGFR cohort (≥90 mL/min: 1.2%–1.3%; 60–89 mL/min: 2.1% versus 2.0%; 30–59 mL/min: 5.8% versus 6.2%; and <30 mL/min: 14% versus 14%, respectively), with no statistically significant increased odds of AKI. Davenport et al. (5) also performed a propensity score–adjusted cohort analysis of 17,652 patients who underwent CECT or unenhanced CT with risk stratification by eGFR. The incidence of AKI was similar between higher eGFR cohorts in CECT versus those in unenhanced CT (eGFR >60 mL/min: 5.4% versus 5.5%; 45–59 mL/min: 10.5% and 10.8%, respectively). In patients with eGFR 30 to 44 mL/min, the incidence of AKI was slightly higher among those with CECT exposure than in those with unenhanced CECT (16.7% versus 14.2%, odds ratio 1.40; 95% confidence interval 0.997–1.970). In patients with eGFR <30 mL/min, however, there was an increased incidence of AKI among those with CECT exposure compared with unenhanced CT (36.4% versus 19.4%, respectively). These studies show similar incidence rates of AKI between CM exposed and unexposed patients with normal or mildly impaired renal function. However, in the Davenport study, the odds of AKI were increased in patients with severe and possibly moderate renal impairment who were exposed to CM. The disparate results between these two studies are likely due to differences in baseline cohort characteristics, differences in propensity score models, and the relatively small number of the highest-risk patients.

These and other propensity score–adjusted studies examining IV CIN have significant limitations. Although propensity score adjustment may reduce selection bias, it is not equivalent to the balance of risk factors achieved in prospective randomized controlled trials. The retrospective basis of propensity score adjustment leaves open the possibility that there are confounders not included in the propensity score models that were considered by clinicians in deciding which patients received CECT or unenhanced CT.

Currently available propensity studies demonstrating equivalence of AKI between groups exposed and not exposed to CM are also limited by the numbers of patients studied who are *truly at increased risk*. Despite the robust number of patients studied, the majority have normal or mildly impaired renal function. In the studies by McDonald et al. (4) and Davenport et al. (5), the proportion of patients with eGFR >60 mL/min were 45% and 79%, respectively. It should not be surprising to any nephrologist that the AKI rates for these two groups were similar, given that it is well established that CM is rarely nephrotoxic in patients with normal or mildly impaired renal function. Conversely, the number of patients in these studies with more severe pre-existing CKD, and thus at higher risk of CIN, was comparatively small, with only 11% of individuals in the study by McDonald et al. (4), and 0.6% of those in the study by Davenport et al. (5), having an eGFR <30 mL/min. Other limitations include failure to adjust for other confounding covariates, including prophylactic strategies, concomitant use of nephrotoxic medications, and volume of CM administered; the inclusion of patients with AKI before CT was performed; and misclassification of comorbidities by International Classification of Diseases 9th edition codes. Furthermore, these studies were composed primarily of inpatients, who are inherently more at risk for AKI from multiple causes; were not adjusted for the clinical indications for the CTs; and did not include assessments for long-term mortality or development of CKD.

In addition to the limitations of the current observational literature, there are other important reasons why physicians should not adopt a cavalier position on the nephrotoxicity of IV CM. Multiple experimental studies have demonstrated CM nephrotoxicity (6). The limitations of these experimental studies notwithstanding, the collective evidence of these studies raises a serious concern about CM nephrotoxicity in humans. Furthermore, AKI in general and from CM specifically has been associated with an increased risk of CKD and long-term mortality, and these associations are supported by experimental studies proving plausible biologic mechanisms for these adverse outcomes (2, 3).

So how should physicians interpret the risk of AKI from IV CM administration in light of recent studies? It is clear that there is a negligible risk for AKI from IV CM in patients with normal (eGFR ≥60 mL/min) or mildly impaired (eGFR 45–59 mL/min) renal function. It is also clear that patients with eGFR <30 mL/min are at greatest risk for CIN and should continue to be classified as such, despite mixed findings of propensity-matched studies. This leaves open the question of how to risk classify patients with eGFR between 30 and 45 mL/min. Although propensity-adjusted studies suggest this group is not at increased risk, there remain lingering concerns over the

methods behind these observational studies. We suggest that risk classification for CM nephrotoxicity should not be based solely on eGFR, especially for patients with eGFR of 30 to 45 mL/min. Physicians evaluating the nephrotoxic risk of CM should take into consideration each patient's unique risk factors for AKI and the benefit gained from a CECT. Resolution of the question of the potential risk of IV CM nephrotoxicity in patients historically considered to be at moderate to high risk will require additional clinical research. Prospective randomized trials will not be possible for ethical reasons. However, observational studies should be conducted in a variety of clinical settings, primarily in patients with eGFR <45 mL/min, with adequate power using methods that adjust for patient differences.

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Contrast-Induced Nephropathy: Is the Concern Exaggerated?

By Teresa K. Chen, MD, MHS, and Derek M. Fine, MD

Intravascular iodinated contrast has historically been considered a risk factor for acute kidney injury (AKI), particularly among individuals with underlying chronic kidney disease (1). Recent studies, however, have suggested that incidence of contrast-induced nephropathy (CIN) may not be as frequent as previously thought (2,3). In this commentary, we argue that contrast material can often be safely used without increased risk of AKI, even among individuals with underlying kidney disease.

Although the definition can vary from study to study (4), CIN is usually characterized by a 0.5 mg/dL rise in serum creatinine from baseline 24 to 72 hours following exposure (1, 3–5). In the clinical setting, CIN is usually a diagnosis of exclusion, as other causes of kidney injury may also manifest during this timeframe. Most studies on CIN, however, do not adjudicate records to confirm diagnosis. Thus, while the occurrence of contrast-associated AKI has been reported to be approximately 8–14% in the context of chronic kidney disease, this is likely an overestimation (3,5,6).

Moreover, patients who undergo imaging tests requiring contrast enhancement often have comorbidities that place them at increased risk for developing AKI. In a retrospective study of over 12,000 propensity score–matched patients who underwent either contrast-enhanced or unenhanced CT scans, McDonald and colleagues reported that incidence of AKI was independent of contrast material exposure (3). In another large study that also utilized propensity score matching, Hinson and colleagues found similar rates of AKI, regardless of baseline kidney function, among 17,934 patients who presented to a large urban emergency department and underwent contrast-enhanced CT (n=7201), unenhanced CT (n=5499), or no CT (n=5234) (2). The use of propensity score matching in these two studies minimized the likelihood of selection bias (2,3). It is interesting that risk factors associated with an increased risk of AKI included older age, administration of nephrotoxins, hypoalbuminemia, history of congestive heart failure, and underlying chronic kidney disease (2).

Certainly, one cannot account for all potential confounders in a retrospective study. Nonetheless, even if residual confounding were to exist, both studies suggest a low risk of contrast-associated AKI (2,3), particularly in the context of intravenous fluid administration (2). It is important to note that the number of patients with advanced chronic kidney disease (defined as a baseline estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) was limited, although even in this group there appeared to be no increase in risk for AKI with contrast-enhanced scans (2,3). The small number exposed, however, suggests that contrast is likely avoided in individuals with most compromised kidney function due to concern for kidney injury.

Even if patients develop AKI following the administration of contrast material, few have persistent renal impairment. In a recent 2 x 2 factorial trial in which 5177 patients undergoing angiography were randomized to receive intravenous bicarbonate versus intravenous sodium chloride and oral acetylcysteine versus oral placebo, 8–9% developed CIN (6). At 90 days, however, only ~1% required dialysis, ~1% had persistent kidney impairment, and ~2% had died. Of note, this trial restricted enrollment to individuals with moderate to severe chronic kidney disease (baseline eGFR of 15 to 44.9 mL/min/1.73 m^2 or eGFR of 45 to 59.9 mL/min/1.73 m^2 with concurrent diabetes mellitus) (6).

Unfortunately, no angiography study can be done without contrast to serve as a control in order to fully delineate the effects of contrast. Also, one might argue that the lack of effect of interventions is in part due to the lack of significant toxicity of contrast in the context of fluid administration. Even in the most frequently used CIN risk prediction model (1), volume of contrast exposure contributes far less to the risk score compared to other clinical factors such as chronic kidney disease, presence of hypotension, congestive heart failure, or diabetes mellitus. Thus, it remains unclear whether kidney injury that occurs following contrast administration is due to the contrast itself or independent of the contrast.

Historical studies reporting an association of contrast material with AKI were done in the context of high-osmolar and ionic forms of iodinated contrast, likely larger infusion volumes, and in the absence of adequate hydration. Findings in these recent studies, with a trend toward the judicious use of safer agents in well-hydrated patients, suggest that the concern for CIN may be significantly less than we have previously anticipated. As such, we conclude that in cases where the administration of contrast is deemed to be likely helpful, we should rethink our risk-benefit analysis when considering risk of CIN.

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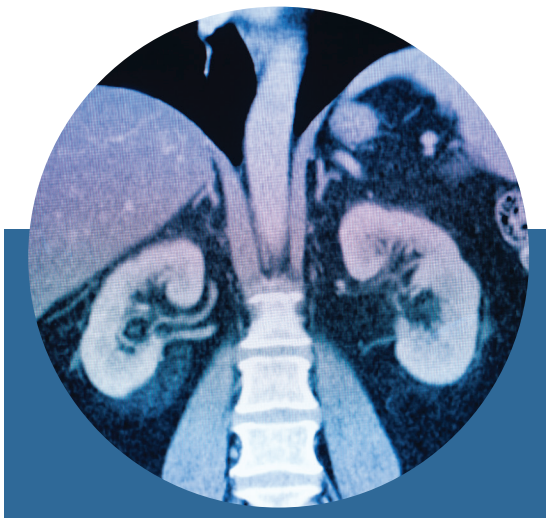

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