

Defining Contrast-Induced Nephropathy

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Clin J Am Soc Nephrol 4: 1151–1153, 2009. doi: 10.2215/CJN.03410509

Contrast-induced nephropathy (CIN) is one of the most common forms of hospital-acquired acute kidney injury (1). The elective or semielective timing of the majority of diagnostic and therapeutic procedures using iodinated contrast allows CIN to be one of the few causes of acute kidney injury that are amenable to implementation of preventive interventions. Numerous potential preventive strategies have been evaluated, including periprocedural administration of saline (2,3) or isotonic bicarbonate solutions (4–7); use of pharmacologic agents including diuretics (2), mannitol (2), natriuretic peptides (8), dopamine (9), fenoldopam (10), theophylline (11,12), and N-acetylcysteine (12–14); and prophylactic renal replacement therapy (15–17). In addition, multiple studies have compared the relative nephrotoxicity of various contrast agents (18–23). In virtually all of these studies, CIN has been defined in terms of small absolute or relative increases in serum creatinine concentration. Implicit in the use of these surrogate end points is the assumption that amelioration of contrast-associated increases in serum creatinine correlates with improved clinical outcomes.

The association between CIN and adverse clinical outcomes, including cardiovascular complications and death, has been amply demonstrated in retrospective database analyses and prospective observational studies (24–28); however, these analyses have not been sufficient to establish a causal relationship. Many of the underlying risk factors for CIN, including diabetes, chronic kidney disease, and diffuse vascular disease, also represent direct risk factors for cardiovascular complications and death. Thus, proof of a causal link must go beyond mere association and also requires demonstration that prevention of CIN decreases these adverse clinical outcomes without modification of other risk factors.

In this issue, Solomon *et al.* (29) attempt to demonstrate this cause-and-effect relationship in a secondary analysis of data from the Cardiac Angiography in Renally Impaired Patients (CARE) Study. The CARE Study was a randomized, controlled trial that compared the rates of CIN associated with the non-ionic, low-osmolar iodinated contrast agent iopamidol and the iso-osmolar agent iodixanol in 414 patients who underwent diagnostic or therapeutic coronary angiography (23). In the

primary analysis of the CARE Study, there was no significant difference in the incidence of CIN, defined either as a ≥ 0.5 -mg/dl increase in serum creatinine (4.4% iopamidol *versus* 6.7% iodixanol; $P = 0.39$) or as a $\geq 25\%$ increase in serum creatinine (9.8% iopamidol *versus* 12.4% iodixanol; $P = 0.44$). In this analysis, Solomon *et al.* attempt to correlate the development of CIN with mortality, ESRD, and cardiovascular complications in the 12 mo after the index angiographic procedure; however, the definitions of CIN that they use for this analysis are different from those prospectively specified for the primary analysis, employing even smaller absolute increases in serum creatinine (≥ 0.3 mg/dl as compared with ≥ 0.5 mg/dl) as well as small relative increases (≥ 15 to $\geq 25\%$) in serum cystatin C. Using these definitions, they have converted a “negative” study to a “positive” one, reporting higher rates of CIN associated with iodixanol administration as compared with iopamidol. They also ascertained 1-yr outcomes in just over 70% of the original study cohort. Death, ESRD, and cardiovascular complications were more common in patients who developed CIN as compared with those who did not and occurred more frequently among patients who were randomly assigned to iodixanol as compared with iopamidol (incidence rate ratio 1.5 for all events [$P = 0.016$]; 3.2 for death, stroke, myocardial infarction or ESRD [$P = 0.024$]).

How is one to interpret these results? The authors conclude that the parallel decrease in the incidence of both CIN and adverse clinical outcomes associated with iopamidol as compared with iodixanol supports a causal role for CIN in the development of these outcomes, but have they truly demonstrated causality? Although in this analysis they report lower rates of both CIN and adverse outcomes in the iopamidol group as compared with iodixanol group, this association did not exist in their primary analysis. Using a more conventional definition, the rates of CIN were similar with both contrast agents, dissociating the differential rates of adverse outcomes from the rates of CIN. In addition, if a true causal relationship is present, then there should be a graded increase in the rate of adverse clinical outcomes as the magnitude of change in the surrogate end point increases. Instead, they report an inverse relationship, with a decline in the incidence rate ratio for death, stroke, myocardial infarction, and ESRD that required dialysis in patients with CIN as compared with those without as the stringency of the definition of CIN increased. Although results of this analysis do not negate a causal relationship, they are insufficient to support one.

Published online ahead of print. Publication date available at www.cjasn.org.

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Solomon *et al.* conclude by suggesting that their results validate the use of these small changes in surrogate markers as primary outcomes in future randomized clinical trials for CIN prevention. Undoubtedly, the use of these more sensitive definitions for CIN will increase event rates, thereby magnifying statistical power and decreasing the apparent sample size needed for clinical trials, but are these surrogate end points truly validated? The CIN literature is already replete with small studies' demonstrating amelioration of the rise in serum creatinine without a clear link to clinically meaningful outcomes. The multitude of small studies has yielded conflicting results and has often confused rather than informed clinical decision making. Rigorous validation of small changes in kidney function as meaningful surrogate end points for CIN will require larger trials—not smaller ones—designed with the statistical power to detect differences in clinically relevant end points. Only then will we be able to sort out the tangled relationship of cause and effect.

Disclosures

None.

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See related article, “Contrast-Induced Nephropathy and Long-Term Adverse Events: Cause and Effect?” on pages 1162–1169.

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