Minimizing the Renal Toxicity of Iodinated Contrast

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A substantial proportion of adults with coronary disease are at risk for contrast-induced acute kidney injury (CI-AKI), manifested primarily by underlying chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL·min⁻¹·1.73m²⁻¹. Although patients commonly understand that they have heart disease, studies have shown that <10% of those with chronic kidney disease are actually aware of this problem; thus, if not emphasized by the cardiologist during the consent before angiography, CI-AKI may come as a surprise to patients and their families after the procedure. All forms of intravascular iodinated contrast are very water soluble, freely filtered by the glomerulus, and avidly taken up by renal tubular cells in the loop of Henle, and are retained in patients with chronic kidney disease within tubular cells and the peritubular space for ~7 days where there is direct oxidative cellular damage, sloughing of renal tubular cells and brush border material, and acute tubular dysfunction. Thus, the interest in reducing CI-AKI and its translation, if any, into improved clinical outcomes after angiography and coronary intervention have long been of interest among interventional cardiologists.

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In the current issue of Circulation are reports from 2 randomized trials using very different approaches in an attempt to reduce CK-AKI. The Acetylcysteine for Contrast-Induced Nephropathy (ACT) Trial Investigators present the largest randomized, placebo-controlled trial to date of short-term, oral N-acetylcysteine 1200 mg twice a day given before and after angiography. In convincing fashion, this high dose of N-acetylcysteine did not reduce rates of CK-AKI (12.7% for both groups) as assessed with a single postprocedural creatinine value at ~58 hours after contrast exposure. The trial recruited moderate-risk subjects (estimated glomerular filtration rate, ~69 mL·min⁻¹·1.73m²⁻¹; ~60% with diabetes mellitus; 100 cm³ of contrast) and was internally consistent, with no significant differences in primary or alternative definitions of CI-AKI or clinical outcomes. The implications of this adequately powered, well-conducted clinical trial are clear: The short-term use of N-acetylcysteine for the prevention of CI-AKI in clinical practice should be abandoned. For researchers, this trial should invoke a check-down on all the reasons for neutral findings, including reconsideration of the therapeutic agent, dose, duration, and measurement of end points. N-acetylcysteine has favorable renal hemodynamic effects, acts as a relatively weak antioxidant, and therefore remains an attractive therapeutic target. Future CI-AKI trials should consider longer treatment periods, more extensive collection of biomarkers, and relevant clinical end points.

The second trial reported in this issue is the Renal Insufficiency Following Contrast Media Administration (REMEDIAL II) trial, which, in high-risk subjects (estimated glomerular filtration rate, ~32 mL·min⁻¹·1.73m²⁻¹; ~70% with diabetes mellitus; ~140 cm³ of contrast) tested a strategy of forced diuresis using large volumes of intravenous crystalloid and low-dose loop diuretic combined with a device (RenalGuard, PLC Medical, Franklin, MA) that controls an intake/output matching algorithm and induces supraphysiological urine flow rates. With this strategy, subjects randomized to the device achieved a urine flow rate of ~350 mL/min compared with an unspecified but expected <150 mL/h in the control group. Using 2 different biomarkers (creatinine and cystatin C) measured at multiple time points out to 7 days, the investigators showed that there were lower rates of CI-AKI (11.0% versus 20.5%; relative risk reduction, 63%; P = 0.025) and clinical events in the experimental arm. This prevention strategy theoretically works to reduce contrast exposure and reuptake by renal tubular cells and to accelerate its urinary elimination. This trial could have been improved with an attempt to measure the radiographic degree of residual contrast in the kidneys and the quantity of contrast removed by urinary losses. If these 2 measures were consistent with the biochemical results, then the therapeutic concept would have been solidified. Considering these shortcomings, the authors and investigators should be congratulated on completing a difficult protocol, addressing safety concerns and logistical difficulties, and bringing a relatively clear result to the clinical and research community. For very high-risk patients, forced diuresis appears to have merit conceptually and is worthy of consideration in a large, definitive-outcomes trial.

In summary, the ACT trial will influence clinical practice by dissuading interventional cardiologists and other operators from the routine use of short-term N-acetylcysteine and stimulate researchers to test antioxidants for much longer durations of therapy to match the time iodinated contrast is present in the renal tubular cells and peritubular space. The REMEDIAL II trial should encourage investigators to consider reducing nephrotoxicity by reducing the transit time and opportunity for tubular uptake of contrast using forced diuresis in patients with severe baseline chronic kidney disease. The forced diuresis approach should be balanced by
the risks of precipitating pulmonary edema or electrolyte shifts with this high-volume/high-output strategy. Finally, future research can be enhanced by creative measures giving insights into mechanism of benefit, by using complementary modalities, and of course by the power of large-scale trials that give valid and definitive results that change clinical practice.10

Disclosures
None.

References

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