All patients would prefer to avoid a complication of a cardiac procedure—thus, discussion of risks of stroke, death, and bleeding resonate with patient-oriented decision-making processes. Contrast exposure may induce a transient decrease in renal function after cardiovascular catheterization procedures. Contrast-induced acute kidney injury (CI-AKI) has been clearly associated with worse cardiovascular outcomes at 1-year follow-up. But, it is difficult to discuss this complication with patients in a meaningful manner: a patient does not feel a creatinine rise of 25% occurring 48 hours after their procedure. Furthermore (1) the definition of CI-AKI is variable,1 (2) prevention strategies remain controversial,2,3 and most importantly (3) the connection between prevention of CI-AKI and improved long-term cardiovascular and renal outcomes is unproven.4

**Defining CI-AKI**

In this study, both the development (n=458) and validation (n=253) sets of this registry analyses demonstrate that for patients at high risk for AKI (estimated glomerular filtration rate ≤30 mL/min per 1.73 m² or Mehran risk score ≥11), CI-AKI can be predicted by the rise of serum NGAL at 6 hours after contrast exposure. At a cutoff value of ≥179 ng/mL, this early measurement had a negative predictive value of >90% with respect to the development of CI-AKI. Furthermore, the negative predictive value was at least as good as cystatin C, and cystatin C did not show its most potent predictive power until 24 hours after contrast media exposure. Based on these promising results, should we abandon creatinine-based definitions of CI-AKI and instead use a simple 6-hour assessment of serum NGAL to define the disease of CI-AKI?

The answer to this simple question is no. Although NGAL rises earlier and lack of NGAL rise has a strong negative predictive value, the positive predictive value is weak: 20%. High NGAL levels occur in the majority of patients, but only 14% of high-risk patients go on to develop a creatinine-based CI-AKI 48 hours after the contrast exposure. As major adverse events are predicted more strongly by a rise in creatinine at 48 hours (hazard ratio, 6.47; 95% confidence interval, 2.19–17.54) than by the NGAL defined 6-hour injury marker nine at 48 hours (hazard ratio, 6.47; 95% confidence interval, 1.43–8.39), it is not clear that there is a prognostic benefit for changing the definition of AKI.

There may be a practical benefit to using NGAL in current clinical practice. In an era of increasing emphasis on early discharge after interventional procedures,9 the 47% of high-risk patients with a normal NGAL level 6 hours after contrast media exposure could be considered reclassified to low risk and allow for earlier discharge. The authors of the current analysis discuss a 1-day increment in length of stay associated with conventionally defined CI-AKI. Although it is tempting to conclude that the current study could remove that 1 extra day of hospitalization, such a conclusion would be premature. The reasons for keeping patients in the hospital to watch for CI-AKI are largely unclear: first, there is no definitive therapy post procedure that prevents the rise of creatinine. Second, the primary treatment strategy for nonoliguric CI-AKI is watchful waiting. Thus, mandatory hospitalization for serial measurements of renal function is of unclear benefit; one can instead imagine patients being discharged with outpatient laboratory testing and readmission for oliguria only. An outcomes-based trial of NGAL-guided versus conventional practice–guided timing of discharge would be needed to determine the exact benefit of this early prognosticator on patient length of stay.

**Is CI-AKI a Disease?**

Although the authors of this study are to be congratulated for defining an early peaking biomarker with additive negative

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**See Article by Quintavalle et al**

In this issue of *Circulation: Cardiovascular Interventions*, Quintavalle et al⁵ provide an assessment of the inflammatory biomarker, neutrophil gelatinase–associated lipocalin (NGAL), as a measure of CI-AKI. NGAL is stored in neutrophil granules and is released in response to inflammation or ischemia: a rise in NGAL is not specific to kidney injury, and elevated NGAL levels have been associated with progression of coronary atherosclerosis and microvascular dysfunction.⁶ Furthermore, NGAL is not the only biomarker associated with increased risk of CI-AKI: a rising serum cystatin C and baseline levels of red cell distribution width also predict increased creatinine 48 hours after angiographic procedures.⁷ But, the authors present a convincing biomarker argument in this registry analyses of 458 high-risk patients: NGAL rises earlier (6 hours post contrast media exposure) than other biomarkers and can thus serve a prognostic role beyond baseline risk scores and other less rapidly rising markers in facilitating the definition and treatment of CI-AKI.

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*Editorial*

**Contrast-Induced Sustained Kidney Injury**

**Defining a Disease**

Harold L. Dauerman, MD
predictive value, there is a larger question that remains in discussing this risk with patients. Is the rise of creatinine 48 hours after contrast exposure by some arbitrary amount (ie, 25% rise compared with baseline or absolute rise of >0.3 mg/dL) an actual disease that patients want to avoid? The current registry confirms the findings of multiple prior registries and clinical trials—if your creatinine bumps, you have more adverse events at 1 year, including death.\(^5\) But, this is confounded by the known risk factors for CI-AKI: look at a risk score for developing CI-AKI and you will find a list of factors associated with worse cardiovascular outcomes.\(^1,2,3\) Thus, the identification of serum NGAL \(\geq 179\) ng/mL 6 hours after contrast exposure is associated with a 2.5-fold increased risk of 1-year major adverse events in multivariable logistic regression models in this study. But there is a missing piece of evidence that patients need: if we blunt the rise of NGAL in these high-risk patients, do they get fewer major adverse events in follow-up? This registry cannot answer that question.

When one reviews the literature on therapies to prevent CI-AKI, they are controversial, inconsistent, and more importantly do not define prevention of a disease. A 48-hour primary end point is the rule for kidney injury trials and thus may at best reflect measures that clearly prevent a transient creatinopathy.\(^4\) Recently, the Bicarbonate or Saline Study (BOSS) findings were published by our investigation group: the inconclusive results of this randomized trial of high-dose bicarbonate versus conventional saline for prevention of CI-AKI will add to the ongoing controversy about optimal prevention strategies.\(^2,5,15\) But, the contribution of BOSS to the literature in this area may be more importantly directed for defining whether CK-AKI is actually a disease. Unlike other trials in this area, the primary end point was a composite of death, dialysis, or a sustained 20% reduction in estimated glomerular filtration rate at 6 months. Bicarbonate did not work better than saline for the primary end point. But, perhaps more importantly, patients developing a conventional 48-hour CI-AKI were found to have a 2.85-fold increased risk of sustained loss of kidney function at 6-month follow-up \((P=0.002\) when compared with those not developing CI-AKI). Quintavalle et al\(^5\) similarly add important information beyond the acute definition and prediction of the creatinopathy state which predominates in most discussions of CI-AKI: 4% of high-risk patients developed sustained reduction in estimated glomerular filtration rate at 1 year, including 3.5% of patients who went on to dialysis. This event rate (3.5% to 4%) may better reflect the development of a clinically relevant disease that should be discussed with patients, as opposed to the much higher values of 10% to 20% for a 48-hour CI-AKI creatinopathy. In the BOSS trial, 21% of patients with 48-hour defined CI-AKI developed a sustained 6-month reduction in estimated glomerular filtration rate as opposed to a 7.5% rate among patients without CI-AKI \((P=0.06)\).\(^15\) Thus, 48-hour CI-AKI should not be seen necessarily as a disease state. Instead, CI-AKI provides us with another clue as to who will actually develop the real disease of contrast injury that would be easily recognizable to a patient—a sustained loss of renal function leading to a higher risk of dialysis.

Future Trials of Contrast-Induced Sustained Kidney Injury

In this light, one can see serum NGAL as one of a series of prognosticators: (1) initial prognostication based on baseline risk factors, various biomarkers, and overall risk score, (2) secondary prognostication based on serum rise in NGAL 6 hours after contrast media exposure, and (3) final prognostication based on 48-hour CI-AKI. But, these measurements provide us with prognostic tools only: future clinical trials may use these acute and subacute markers to help in tailoring therapies early in the hospital course or estimating the time of discharge. But the primary end point of future trials evaluating strategies to prevent contrast media–induced injury need to move from 48 hours to 1 year. We need to prove that blunting the early rise of NGAL or the subacute rise of creatinine makes a difference to 1-year outcomes that are easily recognizable to patients and their physicians. To do this, we will need to start a new era of preventive trials in this area and abandon our exclusive focus on transient AKI. It is time to define the disease and prevention strategies of contrast-induced sustained kidney injury.

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References


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