# Biomarkers of Contrast-Induced Nephropathy

## Which Ones and What Is Their Clinical Relevance?

Jolanta Malyszko, MD, PhD[a,*],
Hanna Bachorzewska-Gajewska, MD, PhD[b],
Slawomir Dobrzycki, MD, PhD[b]

**KEYWORDS**

• Contrast nephropathy • Biomarkers • NGAL • KIM-1 • Cystatin C • L-FABP • NAG

**KEY POINTS**

- Normal serum creatinine has several limitations as a marker for acute kidney injury (AKI), such as wide normal range; gender dependence; and effects of diet, muscle mass, muscle metabolism, drugs, and volume status.
- Biomarkers specific to the kidney can be viewed as belonging to 1 of 2 broad classes representing functional changes (eg, serum creatinine, serum cystatin C, urine output) or kidney damage (eg, proteinuria, urine and serum neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule 1 [KIM-1], liver-type fatty acid binding protein [LFABP]).
- NGAL has several attractive traits, especially its rapid increase in response to kidney injury, typically within 2 to 4 hours. NGAL has clinched status as a promising biomarker for AKI.
- Knowledge about biomarkers has improved substantially, with NGAL being the most studied, followed by KIM-1 and then others.
- The search for "the troponin of the kidney" is far advanced; however, one should be aware that acceptance of troponin as a cardiac marker was also a long process.

*However beautiful is the strategy, you should occasionally look at the results.*
*—Winston Churchill*

## INTRODUCTION

Biomarkers are biological measures of a biological state. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Biomarkers are used to perform a clinical assessment, to monitor and predict health states in individuals or across populations so that appropriate therapeutic intervention can be planned. An ideal biomarker is safe and easy to measure, cost-efficient to follow up, modifiable with treatment, and consistent across gender and ethnic groups. Cardiologists use troponin daily as a biomarker of acute cardiac injury that serves to diagnose, stratify risk, and guide therapy. Therefore, a "troponin-like" biomarker of acute kidney injury (AKI) should be easily measured, unaffected by other biological

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[a] 2nd Department of Nephrology, Medical University, M. Sklodowska-Curie 24a, Bialystok 15-276, Poland;
[b] Department of Invasive Cardiology, Medical University, M. Sklodowska-Curie 24a, Bialystok 15-276, Poland
* Corresponding author.
*E-mail address:* jolmal@poczta.onet.pl

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factors, and capable of both early detection and risk stratification.

## Radiocontrast Media

More than 70 million diagnostic radiographic examinations requiring radiocontrast media (RCM) are performed worldwide each year, with at least 10 million in the United States alone. Procedures using RCM include myelography, angiography (including cerebral arteriography), venography, urography, endoscopic retrograde cholangiopancreatography, arthrography, and computed tomography. Because of the progress in medicine and access to health care, millions of doses of intravascular contrast agents are being administered worldwide, to an increasingly elderly and vulnerable population, many of whom have preexisting chronic kidney disease (CKD) and diabetes mellitus, principal risk factors for contrast-induced nephropathy (CIN). This particular combination creates a "perfect storm" for increased risk and prevalence of CIN. In fact, there is no magical and safe volume of contrast agent to prevent the occurrence of CIN.

The administration of RCM can lead to a usually reversible form of acute renal failure (ie, CIN) that begins soon after the contrast is administered.[1] Most commonly CIN, or contrast-induced acute kidney injury (CI-AKI), is defined as an acute impairment of renal function as manifested by an absolute increase in serum creatinine of at least 0.5 mg/dL or by relative increase by at least 25% from the baseline value.[2] Serum creatinine peaks usually 3 to 5 days after RCM administration and returns to baseline (or a new baseline) within 1 to 3 weeks.[2] CIN is a nonoliguric form of AKI for most patients. In almost all cases, the impairment in renal function is mild and transient. In comparison with percutaneous coronary interventions (PCI), the risk of CIN is low following intravenous contrast administration, even in patients with CKD.[3] As a result of better access to health care, interventional cardiologists are being asked more frequently to perform PCI on increasing numbers of patients with several significant comorbidities such as CKD and/or diabetes mellitus. CIN is a potentially serious complication of PCI.[2] In addition, clinicians are now better informed about the consequences of even small changes in renal function; however, in most circumstances this has not translated into an improvement in the management of AKI, including CI-AKI.[4]

## Markers of Kidney Injury

### Traditional markers

For many years creatinine was the gold standard in the assessment of kidney function and estimation of glomerular filtration rate (GFR). "Normal" serum creatinine has several limitations, such as wide normal range, gender dependence, effects of diet, muscle mass, muscle metabolism, drugs, and volume status, In AKI creatinine levels stabilize within a few days. To date, the loss of kidney function in AKI has been most easily detected by measurement of serum creatinine, which is used to estimate the GFR. However, estimated GFR (eGFR) is of no use in determining kidney function during an acute insult, because up to 50% of kidney function may be lost before an increase in serum creatinine is detected. In addition, after RCM administration resulting in CIN, plasma creatinine concentration usually returns to baseline within 7 days, and less than 1% of patients go on to require chronic hemodialysis. Thus, current biomarkers of kidney injury, especially creatinine and protein in urine, are inadequate.

Creatinine is a poor biomarker for AKI, principally because of its inability to help diagnose the early phase of AKI, including CIN. In addition, creatinine is less accurate for patients with low muscle mass and unusual diets. Other challenges inherent in using creatinine as a marker for AKI, including CIN, may delay diagnosis and potentially misclassify the actual injury status.

Proteinuria is considered a sensitive marker of kidney injury and a means of determining recovery in addition to CKD and its progression. However, it is also not very specific; levels may rise with use of certain nonsteroidal anti-inflammatory medications, neoplasms, lupus, and rheumatoid arthritis.

In summary, neither of these traditional markers reveals the location of kidney injury. Other conventional biomarkers such as urinary casts and fractional sodium excretion have been found to be insensitive and nonspecific for the early detection of AKI. Similarly, other traditional biomarkers detected in urine, such as filtered low molecular weight proteins, tubular proteins, and enzymes, have also suffered from lack of specificity and standardized assays. Thus, different urinary and serum proteins have been intensively investigated as possible biomarkers for the early diagnosis of AKI. The window of opportunity is narrow in CIN, and time to introduce proper treatment after the initiating insult is limited, particularly when patients are discharged within 24 to 48 hours after the procedure. Therefore, there is an extensive ongoing search for potential early markers for AKI, especially in the upcoming setting of short-stay hospitalizations for coronary angiographies and interventions.

### Potential early markers

There are several promising candidate biomarkers with the ability to detect an early and graded