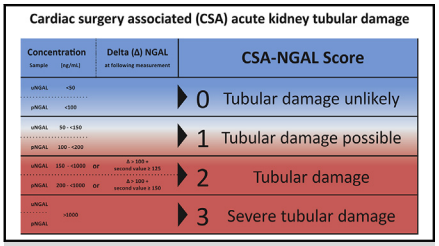
The cardiac surgery–associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage

Hilde R. H. de Geus, MD, PhD,[a] Claudio Ronco, MD, PhD,[b] Michael Haase, MD, PhD,[c] Laurent Jacob, MD, PhD,[d] Andrew Lewington, MD, PhD,[e] and Jean-Louis Vincent, MD, PhD[f]

ABSTRACT

Acute kidney injury (AKI), defined as a rise in serum creatinine (functional AKI), is a frequent complication after cardiac surgery. The expression pattern of acute tubular damage biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) has been shown to precede functional AKI and, therefore, may be useful to identify very early tubular damage. The term *subclinical AKI* represents acute tubular damage in the absence of functional AKI (biomarker positivity without a rise in serum creatinine) and affects hard outcome measures. This potentiates an tubular-damage–based identification of renal injury, which may guide clinical management, allowing for very early preventive-protective strategies. The aim of this paper was to review the current available evidence on NGAL applicability in adult cardiac surgery patients and combine this knowledge with the expert consensus of the authors to generate an NGAL based tubular damage score: The cardiac surgery–associated NGAL Score (CSA-NGAL score). The CSA-NGAL score might be the tool needed to improve awareness and enable interventions to possibly modify these detrimental outcomes. In boldly doing so, it is intended to introduce a different approach in study designs, which will undoubtedly expand our knowledge and will hopefully move the AKI biomarker field forward. (J Thorac Cardiovasc Surg 2016;151:1476-81)



CSA-NGAL score.

Central Message

This paper introduces a biomarker based tubular damage score that constitutes a key paradigm shift in cardiac surgery-nephrology.

Perspective

Identification of cardiac surgery–associated tubular damage with the CSA-NGAL score has the potential to aid the early diagnosis of acute kidney injury. This might enable interventions and therapies to reduce the incidence of cardiac surgery–associated acute kidney injury.

See Editorial Commentary page 1482.

Worldwide, more than 2 million cardiac surgeries are performed each year. Cardiac surgery–associated acute kidney injury (CSA-AKI) is a serious postoperative complication, and is the second most common cause of AKI in the intensive care unit.[1] An incidence of CSA-AKI of up to 39% has been reported, varying depending on patient-related baseline characteristics and the type of surgery.[2] Between 3% and 6.5% of all surgical patients require renal replacement therapy. This worst stage of CSA-AKI is independently associated with a very high mortality rate.[3] Other clinical consequences of CSA-AKI are increased length of hospital stay, increased risk of chronic kidney disease (CKD), and increased risk of death within 5 years after surgery.[4] The success of interventions or new therapeutic strategies aimed at reducing the incidence of CSA-AKI and its related outcomes depends on the optimum time of their application, which is at the very early stages of AKI.

DIAGNOSIS OF FUNCTIONAL AKI

To create uniformity in the diagnosis of AKI, the RIFLE (risk of renal injury/injury to the kidney/failure of kidney function/loss of kidney function/end-stage disease) criteria were proposed in 2004,[5] followed by the Acute Kidney

From the [a]Department of Intensive Care, Erasmus University Medical Center, Rotterdam, The Netherlands; [b]Department of Nephrology Dialysis and Transplantation, International Renal Research Institute, San Bortolo Hospital, Vicenza, Italy; [c]Department of Nephrology and Hypertension, Otto-von Guericke University, Magdeburg, Germany; [d]Service d'Anesthésie-Réanimation, Hôpital Saint-Louis-Assistance-Publique Hôpitaux de Paris, Université Paris 7, Paris, France; [e]Department of Renal Medicine St. James's University Hospital, Leeds, UK; and [f]Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium.

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Address for reprints: Hilde R. H. de Geus, MD, PhD, Department of Intensive Care, Room H-619, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands (E-mail: h.degeus@erasmusmc.nl).

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Abbreviations and Acronyms

AKI = acute kidney injury
AKIN = Acute Kidney Injury Network
CKD = chronic kidney disease
CSA = cardiac surgery associated
eGFR = estimated glomerular filtration rate
KDIGO = Kidney Disease–Improving Global Outcomes
NGAL = neutrophil gelatinase-associated lipocalin
RIFLE = risk of renal injury/injury to the kidney/failure of kidney function/loss of kidney function/end-stage disease
SCr = serum creatinine

Injury Network (AKIN) criteria in 2007[6] and the Kidney Disease–Improving Global Outcomes (KDIGO) criteria in 2012.[7] These criteria express the deterioration of kidney function as a decline in the estimated glomerular filtration rate (eGFR), which is based on an increasing serum creatinine (SCr) concentration and a declining urine output. However, in health, the kidneys have a significant degree of excess capacity, such that 50% of the functional kidney mass can be damaged without any drop in SCr-based eGFR. Therefore, an increase in SCr occurs relatively late after the initial injurious event (24-48 hours), with hemodilution related to pump priming as an additional contributor to this delay.

In view of this limitation of an SCr-based definition of AKI, an additional test indicating that assessment of acute tubular damage might be of value for the clinician. The idea that detection of this so-called "subclinical AKI"[8] (ie, acute tubular damage in absence of an elevated SCr concentration) was recently suggested by the Acute Dialysis Quality Initiative (ADQI)-10 consensus work group.[9] The field of AKI biomarkers is rapidly evolving, and new proteins released by injured tubular cells are constantly being discovered. All of these new biomarkers carry the potential to serve as markers for acute tubular damage in the absence of functional AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is the most well described and studied AKI biomarker in adult patients undergoing cardiac surgery to date, and is our current focus of interest.

NGAL

NGAL is a small siderophoric protein that is intensely up-regulated and excreted in cases of acute tubular damage. It can be detected in both plasma and urine. In the early phases of AKI, NGAL mitigates iron-mediated toxicity by providing a reservoir for excess iron, and in subsequent phases, it promotes regeneration and repair by regulating intracellular iron availability. NGAL is readily filtered in the glomerulus and readily reabsorbed in the proximal tubular segments. Immediately following diverse injurious events, NGAL is up-regulated in the distal parts of the nephron. Consequently, increased levels of plasma and urinary NGAL are detectable, presumably resulting from both apical and basolateral secretion. Impaired proximal tubular reabsorption, due to coexisting or subsequent proximal cellular damage that exceeds the megalin-dependent transport maximum, further potentiates urinary NGAL excretion.[10,11] Although other sources of NGAL exist in various pathological states (ie, inflammation, infection, intoxication, ischemia, and neoplastic formation), a potentiated NGAL response is very discriminative for acute tubular damage, as confirmed by experiments in NGAL-knockout mouse models.[12]

DIAGNOSIS OF ACUTE TUBULAR DAMAGE, OR SUBCLINICAL AKI

Based on the results of a multicenter pooled analysis by Haase et al[8] on the clinical impact of subclinical AKI, defined as NGAL expression in absence of functional AKI, a clear separation in the definition between acute tubular damage and functional AKI seems justified. Acute tubular damage is a pathological process that is separated in time (earlier) from SCr-based dysfunction, which is not always manifested as AKI according to the RIFLE, AKIN, and KDIGO definitions. Nonetheless, the independent presence of acute tubular damage affects patient outcomes and thus should at least be recognized and possibly addressed as a separate clinical entity.[8] We propose the use of NGAL as the biomarker in a new definition of acute tubular damage, the Cardiac Surgery–Associated NGAL (CSA-NGAL) score to further complement the functional diagnosis of AKI.

A PROPOSAL: USE OF THE CSA-NGAL SCORE TO DETECT ACUTE TUBULAR DAMAGE

The CSA-NGAL score (Figure 1) was created by H.R.H.d.G., C.R., M.H., L.J., A.L., and J.-L.V., all experts in the field of critical care and critical care nephrology, after round table discussions. Although the urge to move the field of kidney biomarker research to a different level has been present for awhile, the lack of definite threshold values for biomarkers such as NGAL and a scoring system linked to treatment suggestions has hindered the development of a new scientific approach.

Today, the level of evidence regarding NGAL cutoff values for the detection of acute tubular damage is much higher than that available at the time of the introduction of the RIFLE criteria, which were based on potentially prognostically relevant and memorable SCr cutoff values. Results supporting the prognostic significance of the RIFLE criteria were reported subsequently.[13,14] We propose that the introduction of applicable NGAL cutoff values in the CSA-NGAL score will result in a similar development for the diagnosis of subclinical AKI.

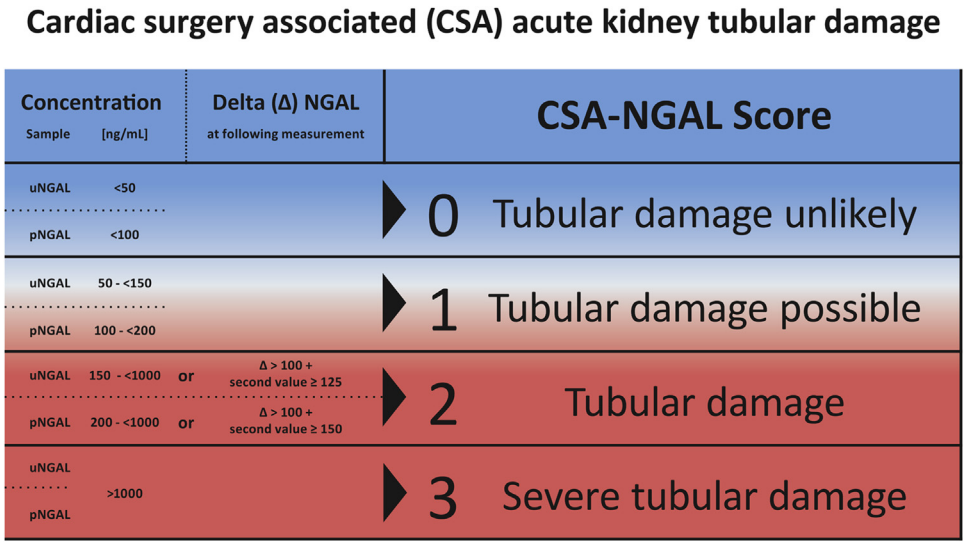

FIGURE 1. CSA-NGAL score. *CSA*, Cardiac surgery associated; Δ*NGAL*, NGAL increase; *CSA-NGAL score*, cardiac surgery–associated NGAL score; *uNGAL*, urine NGAL; *pNGAL*, plasma NGAL.

HOW IS THE CSA-NGAL SCORE DERIVED?

Based on the published observational data and our personal experience, we have suggested potential thresholds to enable standardized research, which remain to be validated in prospective studies. We did this based on the assumption that it has little foreseeable clinical downside.[15] The absolute threshold recommendations for the NGAL cutoff values are based on published values measured using available clinical platforms, including the NGAL Test (BioPorto Diagnostics, Gentofte, Denmark), Triage (Alere, Waltham, Mass), and ARCHITECT (Abbott Diagnostics, Lake Forest, Ill). Accordingly, the 95th percentile of NGAL concentration in healthy persons provided by the platform manufacturers was considered.

For application in clinical research protocols, standardized laboratory platforms are needed to enable generalize ability and comparability of future studies. Acute tubular damage occurs in a continuum, and absolute cutoff values of 150 ng/mL for urinary NGAL and 200 ng/mL for plasma NGAL are reasonable for identifying patients with acute tubular damage related to cardiac surgery or critical illness[16-21] (Figure 1). Such acute tubular damage is associated with a risk of de novo AKI, progression of established AKI, poor recovery of renal function, increased need for initiation of renal replacement therapy, and development of CKD, end-stage renal disease, and eventually death. Delta values should be considered in patients with changes in NGAL concentration in sequential measurements, especially in patients in whom the absolute NGAL value does not exceed the suggested threshold, as well as in patients with preoperative renal impairment.[19] Therefore, it is suggested that increases in urine NGAL concentration >100 ng/mL with the second value ≥125 ng/mL and in plasma NGAL concentration >100 ng/mL with the second value ≥150 ng/mL are indicative of acute tubular damage (Figure 1).

HOW TO INTERPRET NGAL VALUES IN CASES OF PREOPERATIVE RENAL IMPAIRMENT?

Preoperative renal impairment, defined as an eGFR <60 mL/min/1.73 m^2, proteinuria with >30 mg/g creatinine, or a dipstick analysis result >1+, might contribute to elevated plasma NGAL baseline values (209 ng/mL in patients with AKI vs 120 ng/mL in those without AKI).[19] Thus, knowledge of a patient's baseline NGAL value is needed for the subsequent interpretation of values measured during or immediately after surgery. This necessitates the inclusion of delta (Δ) NGAL concentration in the CSA-NGAL score (Figure 1), as well as determination of a preprocedure baseline NGAL value. In contrast, Perrotti et al[22] reported a 6-hour plasma NGAL cutoff value of 155 ng/mL for the presence of AKI in patients with a preoperative creatinine clearance <60 mL/min/1.73 m^2. Several other studies have reported essentially unchanged cutoff values for AKI as well, even in the presence of preexisting CKD.[17,18] At this time, the evidence regarding the impact of renal impairment is at least conflicting, and thus we recommend applying the proposed ΔNGAL thresholds prospectively to generate the data to address these uncertainties.

CSA-NGAL SCORE: POSSIBLE CLINICAL IMPLICATIONS

In current medical practice, patients experience multiple subclinical episodes of acute tubular damage. After cardiac surgery, patients are routinely prescribed diuretics, angiotensin-converting anzyme inhibitors and antibiotics,

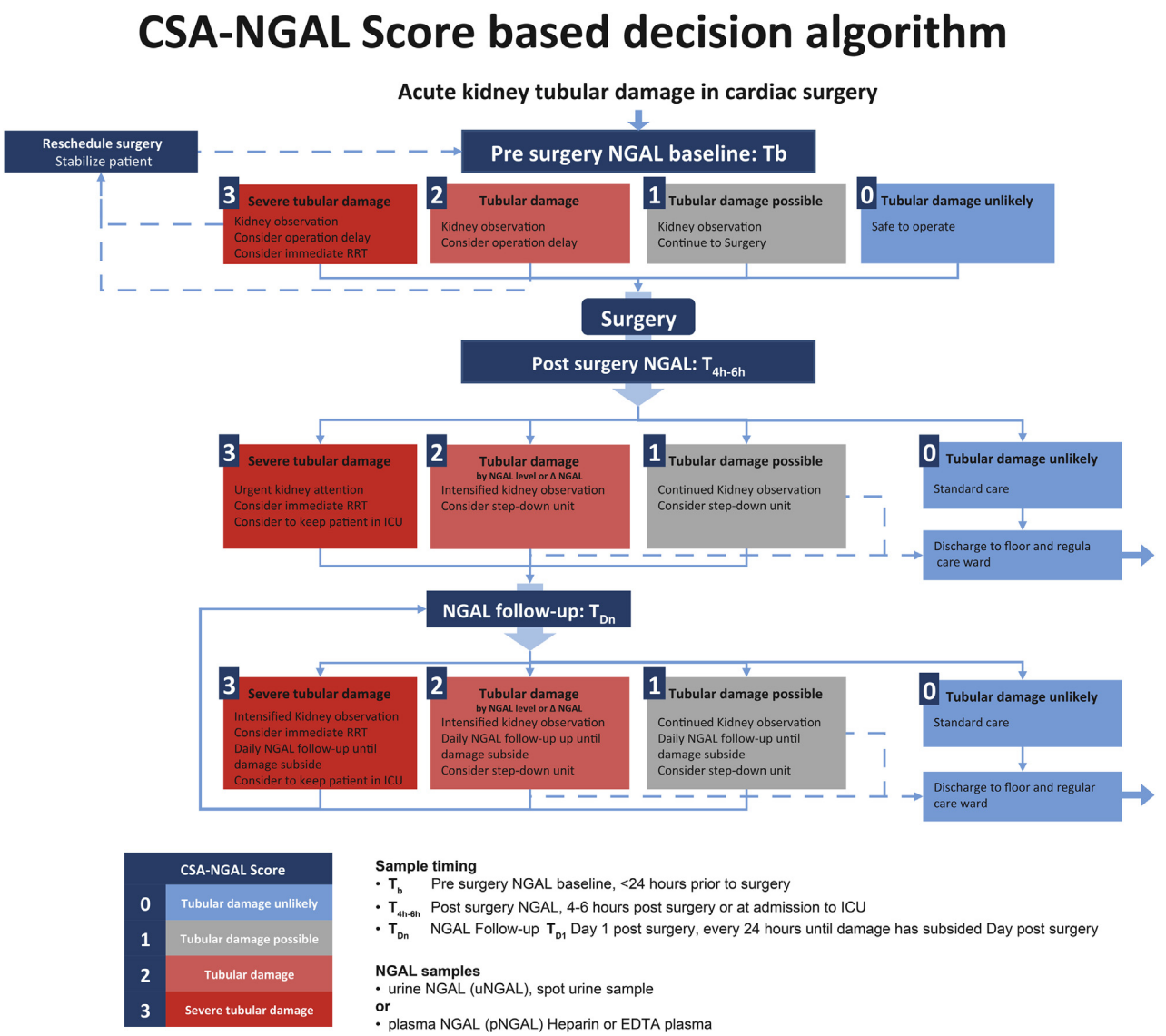

FIGURE 2. CSA-NGAL Score clinical decision algorithm. *CSA-NGAL score*, Cardiac surgery–associated NGAL score; *NGAL*, neutrophil gelatinase-associated lipocalin; *Tb*, baseline; *RRT*, renal replacement therapy; *ICU*, intensive care unit; T_{Dn}, day postsurgery; Δ*NGAL*, NGAL increase; *uNGAL*, urine NGAL; *pNGAL*, plasma NGAL; *EDTA*, ethylenediaminetetraacetic acid.

as required, potentially adding additional insults to undetected acute tubular damage. Application of the CSA-NGAL score can prevent this scenario. A structured preoperative risk assessment to assess a patient population at high risk for AKI is desirable as well.[23] Baseline measurements can aid in preoperative risk assessment, and elevated NGAL values may even suggest postponing surgery until kidney function can be optimized and additional insults avoided[18,24] (Figures 2 and 3). This concept is supported by the findings of Di Somma and colleagues,[20] who reported improved prognostication of kidney damage and overall related outcomes when NGAL measurements were added to the clinical assessment. Prospective observational and intervention studies are needed to apply the CSA-NGAL score as a clinical tool to enable a more precise estimation of the incidence and impact of subclinical AKI. In our view, this is the only way to answer the questions of whether routine use of NGAL as a biomarker can offer additional value in patient care, which is the only way to push AKI-related biomarker research to the next level.

SEQUENTIAL MEASUREMENTS

The dynamics of NGAL in patients undergoing cardiac surgery have been carefully documented over the past decade. A clear relationship is evident between pump run and acute tubular damage; therefore, the temporal assessment of biomarkers is likely to have value for clarifying prognostic uncertainty. Based on the available evidence,

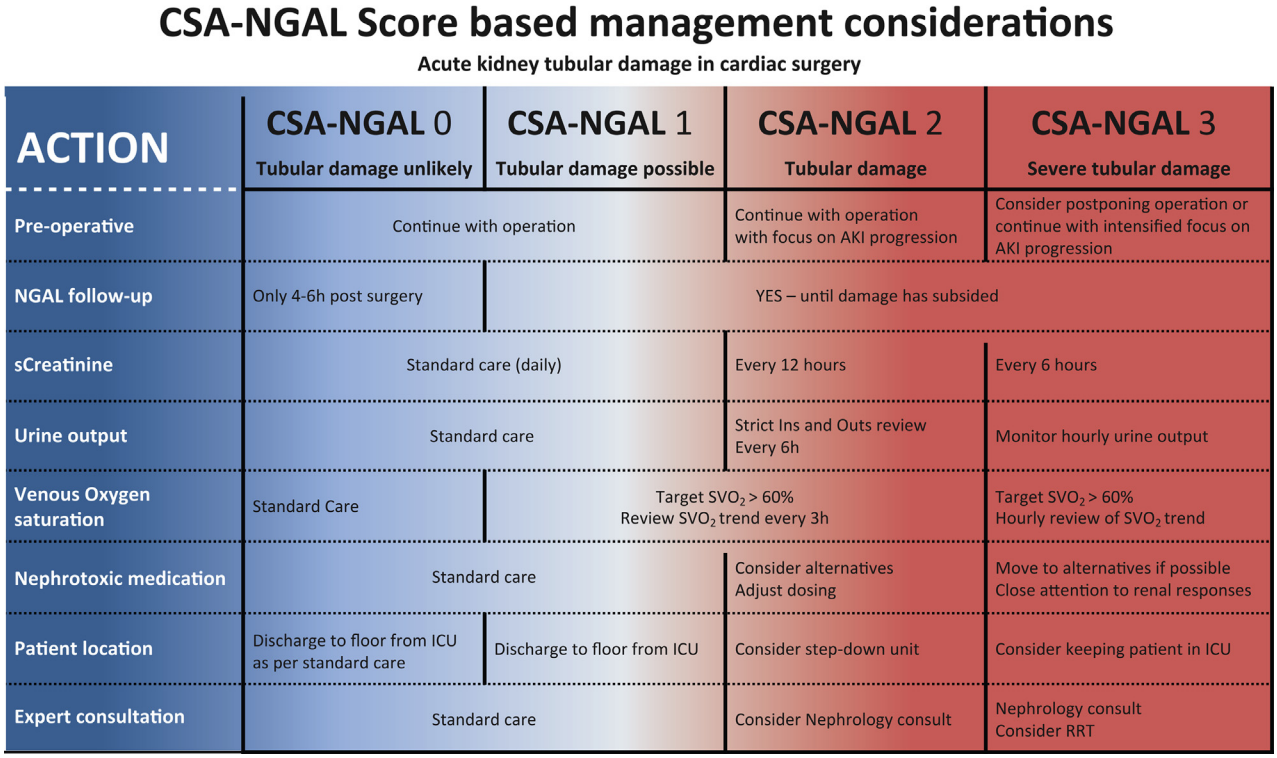

FIGURE 3. Clinical management considerations in patients admitted for cardiac surgery. *CSA-NGAL score*, Cardiac surgery–associated NGAL score; *AKI*, acute kidney injury; *NGAL*, neutrophil gelatinase-associated lipocalin; *SvO_2*, central venous oxygen saturation; *ICU*, intensive care unit; *RRT*, renal replacement therapy.

the optimal times for NGAL measurements are the day before surgery, during surgery, and the day after surgery. The baseline urine or plasma value would be presurgery (within 24 hours before the procedure), following by values obtained at 4 to 6 hours after the commencement of surgery (knife to skin) and at day 1 postsurgery (within 6-12 hours after returning to the intensive care unit).

ADDITION OF THE CSA-NGAL SCORE TO RIFLE, AKIN, OR KDIGO SCORES

The CSA-NGAL score has the capability of identifying tubular damage in patients not yet displaying clinical dysfunction (RIFLE stages R-F, AKIN stages 1-3, or KDIGO stages 1-3). This early detection of acute tubular damage preceding functional loss could trigger appropriate therapeutic modifications (Figure 3). Furthermore, the CSA-NGAL score can help rule out acute tubular damage in patients with preexisting chronic dysfunction (elevated SCr, no rise in NGAL) or in patients experiencing a simple functional adaptation to hypovolemia without acute tubular damage (elevated SCr, no rise in NGAL).

URINE OR PLASMA NGAL?

The current evidence shows no superiority of urine NGAL over plasma NGAL measurements or vice versa in AKI predictive ability, and thus either may be used according to hospital preference and availability. Switching between urine and plasma measurements is not advisable, however, given some baseline and range differences.

PERSPECTIVE

We propose the application of the CSA-NGAL score in prospective studies with adults undergoing cardiac surgery in addition to a functional score for AKI (RIFLE, AKIN or KDIGO). Acute tubular damage without functional AKI (ie, subclinical AKI) affects hard outcome measures, and the recognition of its presence has the potential to facilitate the earlier implementation of interventions or precautions to prevent further damage and/or progression to functional AKI.

The prevalence of functional AKI is estimated to be considerably higher than previously thought, with 80% of cases not captured in routine hospital data.[25] The consequential economic impact of this estimate in terms of excess inpatient deaths and associated morbidity is huge and justifies increased awareness of the disease, including the clinical signs that may precede it.[25] The CSA-NGAL score might be the tool needed to improve awareness of acute tubular damage, which will allow for early interventions to possibly modify these detrimental outcomes.

Although use of the CSA-NGAL score might be challenging and bold based on the available literature, we believe that there is an urgent need to do so. In our view,

further biomarker studies that will show slight area under the curve improvements and slightly different optimal cut-off values in the prediction of CSA-AKI will not add any new insights. Moving forward from what we already know will require changing clinicians' mindset, as well as the approach to study design. In boldly doing so, we will expand our knowledge of biomarkers and assess the prospects of further progression in the field. An early diagnosis of acute tubular damage might increase the effectiveness of therapies and interventions. The CSA-NGAL score will undoubtedly need to be reevaluated and refined in the near future as new data become available.

In conclusion, we have constructed a bridge between science and a possible clinical application for NGAL. It is time to recognize that for a defined patient population at high risk for procedure-related functional AKI, acute tubular damage may occur before dysfunction becomes apparent. This subclinical AKI is a separate entity that should trigger awareness and clinical interventions. The measurement of NGAL in this setting will act to support other available clinical information in patient management and generate prospective knowledge of a different level than that currently available.

Conflict of Interest Statement

H.R.H.d.G. has received travel and lecture reimbursements from Alere and BioPorto. C.R. has received honoraria from Alere, Asahi, Astute, and BioPorto and from GE, Baxter, and Fresenius for lecturing. M.H. has received travel and lecture fee reimbursements from Abbott Diagnostics, Alere, Roche, BioPorto, and Astute Medical. L.J. has received honoraria from Abbvie, Alere, BioPorto, and Fresenius. A.L. has received honoraria from Abbvie, AM Pharma, and BioPorto and from Abbvie, Baxter, and Fresenius for lecturing. J.-L.V. has nothing to disclose with regard to commercial support.

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Key Words: CSA-NGAL score, NGAL, AKI, subclinical AKI, ICU, cardiac surgery