The cardio-renal syndrome (CRS) manifests a complex pathophysiology with dismal clinical outcomes. The proposal of a comprehensive definition that incorporates first the bidirectional nature of the organ interaction and the multiplicity of compensatory mechanisms involved represents a significant paradigm shift. A recent review by Bock and Gotlieb explored this interaction with discussion of novel therapeutic strategies. What appears lacking, however, are options on the diagnostic side. Unfortunately, the majority of heart failure trials excluded patients with significant renal dysfunction (serum creatinine [SCr] range, 151-300 μmol/L). This has led to prescription of morbidity and mortality-lowering pharmacologic agents at lower rates, often with prescription rates differing by stages of chronic kidney disease (CKD). Furthermore, prognosis appears affected by underdetection of admission renal function, underdetection of renal function, with even small decrements of renal function in the hospital and underprescription of proven therapy. However, appropriate prescription may negate this risk. Although novel approaches as suggested by Bock and Gotlieb are timely and needful, recent trials in this area have been disappointing. It is evident that patients are undertreated, more likely to have medications ceased, and more prone to secondary risks and reduced efficacy of device therapy and without proven novel therapies. The issues have raised a call for a modified approach to CRS. First, one that requires alteration in the temporal profile of diagnosis closer to the event rather than a delayed retrospective approach with SCr. Second, greater precision in the evaluation of glomerular filtration rate (GFR), which will generate sound clinical decisions and aid prescribing practices. On the cardiovascular (CV) front, advancements in biomarkers, imaging modalities, and invasive monitoring has allowed us to accurately measure CV function. However, the assessment of renal injury and function is complex and even more so in the CV population. The multiplicity of compensatory mechanism and our inability at present to provide a comprehensive cardio-renal assessment incorporating the dominant etiology or compensatory feedback highlight reasons why renal deterioration often may appear idiosyncratic. Because cardio-renal epidemiology and therapeutic perspectives are well established, this review focuses briefly on concepts in CRS physiology with a focus on the pitfalls of current measures of renal function (RF),
and the status of novel diagnostic tools for assessment of RF in CRS.

CURRENT INSIGHTS INTO PATHOPHYSIOLOGY OF CRS AND ITS CLINICAL IMPLICATIONS FOR PHYSICIANS

Cardio-Renal Pathophysiology

The cardio-renal interaction is primary via the circulatory system (hemodynamic factors) or secondary to underlying endogenous humoral or exogenous factors that are associated with disease of either organ or a combination of both (Figs. 1 and 2). This interaction can occur in normal organs (acute dysfunction) or diseased organs (acute or chronic dysfunction), and in one or both organs or a combination. The causation and temporality of this interaction in terms of kidney damage and subsequent clinical deterioration is unpredictable. This is compounded by a lack of symptoms, the unpredictable time lapse between injury and clinical manifestation, and the narrow therapeutic window between insult and implementing renal protective strategies. Importantly adequacy of RF may be a primary determinant of compensation in patients with heart failure (HF), and therapy capable of improving RF may delay progression of HF.13-17

Intricacies of Renal Blood Flow

Medullary and cortical nephrons share differential blood flows to maintain a corticomedulary solute gradient. Despite receiving 25% of cardiac output, only 10% supply the medulla. The juxtamedullary cortex and outer medulla receive the majority of renal blood flow. With greater density of neural innervations it can modulate acute changes. The precise mechanisms that regulate medullary blood flow (RBF) are unknown, but evidence supports a lack of counter-regulatory control in normal physiology. Supraphysiological sympathetic activation and nitric oxide deficiency, states synonymous with cardiac and renal failure, may however have implications for medullary blood flow. Evidence also builds for the continuity of local and systemic microvasculature. This implies that microvascular disease in individual glomeruli could individually affect compensatory measures with several implications: first, the kidney is highly sensitive to even minor changes in blood flow and, second, the importance of maintaining renal perfusion across the entire vascular bed.18-22

Relationship of Renal Blood Flow and GFR

GFR represents the net filtration of all functioning nephrons. RBF is the most important contributor of GFR

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Acute Cardio-Renal (Type 1)</th>
<th>Chronic Cardio-Renal (Type 2)</th>
<th>Acute Renal-Cardiac (Type 3)</th>
<th>Chronic Renal-Cardiac (Type 4)</th>
<th>Secondary CRS (Type 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ failure sequence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>Acute decompensation of heart function (AHA ACS) leading to kidney injury and/ or dysfunction</td>
<td>Chronic abnormalities in heart function (CHF-CHD) leading to kidney injury or dysfunction</td>
<td>Acute worsening of kidney function (AKI) leading to kidney injury and/or dysfunction</td>
<td>Chronic kidney disease (CKD) leading to kidney injury, disease and/or dysfunction</td>
<td>Systemic conditions leading to cumulative injury and/or dysfunction of heart and kidney</td>
</tr>
<tr>
<td>Primary events</td>
<td>Acute heart failure (MI) or Acute Cardio-Renal Syndrome (ACS) or Cardiogenic Shock</td>
<td>Chronic heart disease (LV remodeling and dysfunction), abnormal glomerular filtration (chronic abnormalities in cardiac function, cardiomyopathy)</td>
<td>Acute Kidney Injury (AKI)</td>
<td>Chronic Kidney Disease (CKD)</td>
<td>Systemic Disease (Sepsis, amyloidosis etc)</td>
</tr>
<tr>
<td>Criteria for primary events</td>
<td>ESC, AKIN, ACC</td>
<td>ESC, AKIN, ACC</td>
<td>RIFLE, AKIN</td>
<td>KDOQI</td>
<td>Disease-specific criteria</td>
</tr>
<tr>
<td>Secondary events</td>
<td>Acute Kidney Injury (AKI)</td>
<td>Chronic Kidney Disease (CKD)</td>
<td>AKI, ACS, arrhythmia, shock</td>
<td>CHD, LV remodeling and dysfunction, diastolic dysfunction, abnormalities in cardiac function, AKI, ACS</td>
<td>AKI, CHD, CKD</td>
</tr>
<tr>
<td>Criteria for secondary events</td>
<td>RIFLE, AKIN</td>
<td>KDOQI</td>
<td>ESC, AKIN, ACC</td>
<td>ESC, AKIN, ACC</td>
<td>ESC, AKIN, ACC, RIFLE/ AKIN, KDOQI</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>Troponin, CK-MB, BNP, NT-proBNP, MPO, IL-6</td>
<td>BNP, NT-proBNP, CRP</td>
<td>BNP, NT-proBNP, CRP</td>
<td>BNP, NT-proBNP, CRP</td>
<td>CRP, procalcitonin, BNP</td>
</tr>
<tr>
<td>Renal biomarkers</td>
<td>hs-CRP, CysC, Urea, Uric Acid, Creatinine</td>
<td>hs-CRP, CysC, Urea, Uric Acid, Creatinine</td>
<td>hs-CRP, CysC, Urea, Uric Acid, Creatinine</td>
<td>hs-CRP, CysC, Urea, Uric Acid, Creatinine</td>
<td>hs-CRP, CysC, Urea, Uric Acid, Creatinine</td>
</tr>
<tr>
<td>Prevention strategies</td>
<td>Acute decompensated heart failure and acute coronary syndromes are most common scenarios.</td>
<td>Ischemic events may be acute coronary syndromes, poorly targeted border pressure, and noncompliance with medication and dietary salt intake.</td>
<td>Randomized trials improving compliance with heart failure care management have reduced rates of hospitalization and mortality, and a reduction in the rates of Acute Cardio-Renal (Type 1) can be inferred.</td>
<td>A common pathophysiologic (hemodynamic, inflammatory, oxidative injury) could be at work to create organ dysfunction.</td>
<td>The chronic processes of cardiac and renal failure, hypertension, vascular stiffness, chronic Na and volume overload, and other factors (neurohumoral, inflammatory, oxidative injury) could be at work to create organ dysfunction.</td>
</tr>
<tr>
<td>Management strategies</td>
<td>Specific – depends on precipitating factors.</td>
<td>Insulin resistant – suppressors, diet, weight and physical competition, pulmonary embolism, posttraumatic adaptive, and other factors left from heart failure, low cardiac output or complication according to RIFLE, AKA, or KDOQI.</td>
<td>Extracorporeal ultrafiltration.</td>
<td>Treat CHF according to ESC guidelines, exclude precipitating factors (hypertension, diabetes mellitus, and others), adjust therapy accordingly and world nephropathy whilst monitoring renal function and electrolytes.</td>
<td>Extracorporeal ultrafiltration.</td>
</tr>
</tbody>
</table>

Figure 1. Classification of CRS. Reprinted with permission from Ronco et al.14
in patients with congestive heart failure (CHF) on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. There is a parallel decline in GFR with declining RBF despite having a stable filtration fraction over almost the full range of RBF. Individual nephrons contribute to total GFR via their single-nephron GFR (SNGFR), described by the following equation:

$$\text{SNGFR} = \frac{k_f \times \Delta P}{H_1}$$

Accordingly, changes to $k_f$ and/or $\Delta P$ will affect renal function. Alteration in RBF can modify $\Delta P$ and glomerular hypertrophy, $k_f$. For example, focal glomerular disease with scarring will reduce the capillary filtration area. In compensation, an increase in blood flow (via afferent arteriolar vasodilatation) and filtration pressure (via efferent arteriolar vasoconstriction) and glomerular hypertrophy in the remaining intact nephrons can stabilize GFR. In addition, GFR is determined by various intrarenal and extrarenal factors, for example, prerenal (cardiac pump failure, excessive vasoconstriction, hypovolemia, pregnancy, and drug therapy), renal (afferent and efferent capillary flow and intrinsic renal disease), or postrenal (increased venous filling pressures) factors. This makes GFR an insensitive marker to detect onset, follow-up
progression or remission in early renal disease, or establish differential diagnosis.  

**Heart Failure and GFR**

In HF renal perfusion, filtration coefficient and compensatory changes (hyperfiltration, hypertrophy, and sclerosis) are affected by many factors, for example, systemic hypertension (diastolic heart failure), systemic hypotension (systolic heart failure), advanced disease (hyperalbuminemia and altered oncotic pressure), and comorbidities such as diabetic nephropathy (underlying glomerular disease). Single nephron glomerular filtration rate (SNGFR) is critical in maintaining overall RF. Many CHF patients have baseline renal impairment, and already may have single nephron filtration fraction (SNFF) and SNGFR functioning at capacity. To compensate for the inability to predict corticomedullary compensation or monitor the many factors threatening to diminish RBF, the ability to anticipate injury and thus potential renal insufficiency is a great armament for early intervention.

**MEASURES OF RF AND THEIR LIMITATION IN HF**

SCr, the dominant marker for clinical RF assessment, usually is produced at fairly constant rates. Excretion occurs predominately by filtration; however, distal tubular secretion may account for up to 10% to 40%. In addition, delays in achieving steady state (which may take up to 7 days) and varying levels make it an unreliable measure for accurate and temporal information. SCr is at best a retrospective window for renal injury and dysfunction.  

GFR, considered the best overall measure of RF, can be estimated from SCr and demographic and clinical variables, such as age, sex, ethnicity, and body size. Physiological decline with age (1 mL/min/1.73 m²/y after 40 years) needs to be taken into account. Alternative measures using an ideal filtration marker (eg, inulin) or an alternative exogenous marker (eg, iothalamate, 51Cr-ethylenediaminetetraacetic acid, technetium-99m, diethylene triamine pentaacetic acid, and iohexol) are cumbersome and not clinically viable choices. Estimated GFR (eGFR) based on an endogenous marker is extremely useful in daily clinical practice, and recent studies have validated these as providing reliable estimates of actual GFR. Other indices of altered RF (eg microalbuminuria and overt proteinuria) are independent predictors of CV morbidity and mortality but are plagued with poor sensitivity and specificity.

**Measures of eGFR**

Two equations, the Cockroft–Gault (C+G) and the Modification of Diet in Renal Disease (MDRD), predominate. Unfortunately, neither of these equations has achieved an optimal mix of accuracy and precision. Noticeable discrepancies have been observed within higher and lower GFRs and among the elderly receiving long-term convalescence, in addition to missing a consistent proportion of cases with renal failure when they are admitted. There are limitations to general use of these estimates.

The C+G formula does not adjust for body surface area but accounts for an increase in creatinine production with weight, and a decrease with age and female sex. In the MDRD study iothalamate was administered to determine GFR in individuals aged 18 to 70 years with chronic, mostly nondiabetic, renal disease with a mean GFR of 40 mL/min/1.73 m². An initial six-variable equation was derived. In the study, 91% and 98% of the GFR estimates were within 30% and 50% of actually measured values and hence were more precise than measured or C+G estimated creatinine clearance. A simplified version was published later. These studies, however, were conducted in controlled settings, leaving questions of generalizability. For example, in a recent study of 2,300 patients with measured GFR values between 24 and 48 mL/min/1.73 m², the MDRD equation was superior to the C+G estimate, however, only 63% to 83% of the estimated values were within 70% to 130% of the measured GFR, leaving one third to one fifth of the population with eGFR values outside this range.

Several additional points are worthy of consideration. Imprecision increases when GFR is severely reduced or at high levels, in hospitalized subjects, in renal transplant recipients, in obese patients, the elderly, specific ethnicities, pregnant patients, in patients with liver disease, and with variations in muscle mass. The formulae are also not validated in subjects with GFR values greater than 60 mL/min/1.73 m² and the National Kidney Disease Evaluation Program recommended that these values should be reported as greater than 60 mL/min/1.73 m² and not as an exact number. Another issue is the difficulty to correctly measure creatinine level. The alkaline picrate (“Jaffe”) assay is subject to interference by noncreatinine chromogens, causing overestimation of SCr of up to 20%. Because these chromogens do not accumulate in renal failure their relative effect is greater at the lower ranges of SCr. Enzymatic assays avoid this interference; however, they should be traceable to the gold standard isotope-dilution mass spectrometry (IDMS) method. Unfortunately, large interlaboratory assay variations are still reported. In addition, the MDRD, but not C+G, equation has been adapted to these new assays. Today, most laboratories use a preferred equation for eGFR and this needs to be considered when making decisions on HF therapy.

On a promising note, Matsushita et al recently published data suggesting a new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that more appropriately categorizes individuals with respect to long-term risk compared with the MDRD equation. Supportive literature has suggested that this equation is currently the most accurate method for estimating GFR for diverse populations. However, of the low number of
patients presenting with eGFR greater than 60 mL/min/1.73 m², no measurement of albuminuria, lack of extremes of age, diverse clinical comorbidities, as well as no comparison with the C+G equation remain limitations at present.43,44

**Formulae Estimating RF in HF Trials and Pitfalls**

Lessons from HF studies suggest that with increasing HF severity, SCr-based formulas and creatinine clearance corrected for body surface area appear to be more precise and accurate. The MDRD formula appears the most precise and has good prognostic value, whereas the sMDRD is slightly less accurate but uses fewer parameters, which makes it a practical alternative in clinical practice. The MDRD equation also has a higher performance in predicting a GFR less than 60 mL/min/1.73 m².45-49 These studies, however, used a single measurement of SCr among clinically stable outpatients. Of concern, when applied in acute coronary syndromes, disagreements occurred in 20%, affecting dosing adjustments. The C+G formula was preferable in small, female, or elderly patients.50

Finally, in relation to therapy, neurohormonal blockade is the only effective noninvasive therapy for CRS presently. Angiotensin-converting enzyme inhibitors, angiotensin receptor antagonist, epinephrine, and endothelin are the agents that are prescribed to preserve renal function when the organs fail in isolation, but are quick to be removed when both organs fail together. More novel concepts and role for inflammation and oxidative stress are evolving but remain distant in relation to translation from the bench to bedside. In both acute and chronic situations, an appreciation of the interaction between heart and kidney during dysfunction of each or both organs has practical clinical implications. If SCr-based eGFR values are to be used in future longitudinal studies the effects of the intervention on creatinine generation, secretion, and extrarenal elimination should be explored. For example, in the MDRD study dietary protein restriction significantly lowered creatinine generation. By the end of the study, the low-protein diet had significantly slowed the mean increase in SCr but did not significantly affect the mean decline in true GFR measured by gold standard techniques.38 This needs to be considered, particularly in unstable patients with fluctuating daily weights and in those in whom SCr level has not reached steady state.

In short, although GFR is more predictive of mortality than the degree of left ventricular dysfunction in patients with CHF, there is, however, no single test that accurately reflects overall RF. The National Kidney Foundation advocates the use of eGFR using the MDRD formula for all patients with renal insufficiency because age, sex, race/ethnicity, and body habitus all significantly affect SCr level.28 More importantly, although eGFR provides the best estimate for RF it cannot be used as a surrogate to detect acute kidney injury (AKI). It can be used only in steady conditions and this is particularly relevant in CRS types 2 and 4.1 Thus, improving RF assessment pushes us further away from renal injury detection.

**MEASURES TO CLOSE THE GAP**

Morrow and de Lomos51 set out three criteria a biomarker should fulfill to be useful clinically. First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and, finally, knowing the measured level should aid in clinical decision making.51,52 We explore five promising biomarkers that may prove beneficial for CRS (Table 1).53-66

**Novel Assessments of Renal Function (Cystatin-C)**

Cystatin C (Cys-C), an endogenous proteinase inhibitor of low molecular weight (13-kDa), possesses many features that make it attractive as a surrogate marker of RF and eGFR. It is synthesized and released into plasma by all nucleated cells at a constant rate, is freely filtered by the glomerulus, and is completely reabsorbed by the proximal tubules. It can be measured easily in the serum and plasma without the need for a urine sample or complex equations. It is not affected by changes in body mass, nutrition, age, or sex, making it potentially more beneficial in critically ill patients, the elderly, and children. It has been validated as a marker of GFR in patients with pre-existing renal dysfunction, and AKI because levels increase before SCr levels increase.22,67-73 In congestive heart failure Cys-C was superior to SCr-based estimates, which underestimate GFR.74 This appears to extend to acute decompensated heart failure admissions without advanced RF.75,76 Cys-C also reflects myocardial stress and damage,77 reflects more advanced left ventricular diastolic and right ventricular systolic dysfunction, and is an independent predictor of long-term prognosis after adjusting for myocardial factors.78 The Cys-C advantage over SCr appears larger and more conclusive in the ability to rule-in renal insufficiency in affected patients.67 Other benefits include predicting future CV events in intermediate-risk individuals, mainly through the identification of those unlikely to develop events.79 it is a stronger predictor of adverse events than conventional measure of RF, and in combination with cardiac troponin T and N-terminal–pro-brain natriuretic peptide it improves risk stratification for CV mortality (inclusive of HF) beyond models of established risk factors.74,80-82

Cys-C should not be interpreted purely as a marker of GFR. Several issues need resolution before its regular use in mainstream. In the elderly, Cys-C estimated substantially larger declines in RF than creatinine.93 Physiologically, Cys-C is a modulator of immune function and serum levels have been found to correlate with C-reactive protein concentrations and immunosuppressant therapy because levels may increase independent of C-reactive protein, further clarification is needed.79,84 Other factors,
### Table 1. Conventional and Novel Biomarkers for Renal Assessments

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Source</th>
<th>Sample Source</th>
<th>Conditions:</th>
<th>Reference Range/Cut-Off</th>
<th>Clinical Outcomes/AUC CPB CIN Tx-DGF ICU/Emergency</th>
<th>Potential Confounders (increase)</th>
<th>Indication For Use From Early Studies: Type of AKI-Associated Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>Amino acid derived</td>
<td>Blood</td>
<td>CPB, CIN, Tx, ICU/Sepsis*</td>
<td>0.8-1.2 mg/dL (male)</td>
<td>Predicts d, S, H, D in all conditions (0.694)</td>
<td>Young, male, body size, meat, drugs, exercise, ethnicity, assay</td>
<td>All</td>
</tr>
<tr>
<td>eGFR-creatinine</td>
<td>As above</td>
<td>Urine</td>
<td>All</td>
<td>80-139 mL/min</td>
<td>Predicts d, S, H, D in all conditions</td>
<td>Young, male, body size, meat, drugs, exercise, ethnicity, technical (formula used), assay</td>
<td>All</td>
</tr>
<tr>
<td>Blood urea</td>
<td>Low molecular weight</td>
<td>All</td>
<td>7-20 mg/dL</td>
<td>Predicts d, S, H, D in all conditions</td>
<td>Dehydration, diet protein, illness, GIT bleed, drugs</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Circulating albumin</td>
<td>&lt;150 mg</td>
<td>Does not predict acute conditions; useful as a marker of risk of CRF and disease progression in association with varying chronic disease (150 mg);</td>
<td>Sex, old age, smoker, inflammation, ↑T4, ACS, CAD, critical illness</td>
<td>Establish diagnosis and follow course</td>
<td>Treatment response</td>
<td></td>
</tr>
<tr>
<td>Cys-C</td>
<td>Extracellular cysteine protease inhibitor, nucleated cells, constant</td>
<td>P/S</td>
<td>12,§ 8, V, 48</td>
<td>&lt;50.0-0.53-0.92 mg/L; (M) &gt;50-58-1.02 mg/L; (M) &gt;45 y (F) &lt;45 y (F) &lt;0.95 mg/L, &gt;45 y &lt;1.20 mg/L (F)</td>
<td>AKI in several settings, but minimal data on specific outcomes Improved detection of GFR in several groups, predicts mortality when used as an estimate of GFR (0.927)</td>
<td>Ischemic, nephrotoxins, cisplatin, septic, CABV, ICU, renal Tx</td>
<td></td>
</tr>
<tr>
<td>NGAL</td>
<td>Iron-transporting protein induced in distal tubule, collecting duct</td>
<td>P</td>
<td>2, 4, NT, 48</td>
<td>190 ng/mL (blood)</td>
<td>d, S, H, D</td>
<td>Infarction, Malignancy, sepsis, CAD, UTI</td>
<td>Ischemic, nephrotoxins, cisplatin, septic, CABV, ICU, renal Tx</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Cell membrane glycoprotein in proximal tubule</td>
<td>NT</td>
<td>12-24, NT, NT,</td>
<td>59-2,146 pg/mL</td>
<td>NA (0.83)</td>
<td>CKD, malignancy, UTI</td>
<td>Ischemic, nephrotoxins, prox tubule, ATN</td>
</tr>
<tr>
<td>IL-18</td>
<td>Proinflammatory cytokine</td>
<td>P/S</td>
<td>4-6, NT, 12, 48</td>
<td>&gt;75 pg/mL</td>
<td>D (0.75)</td>
<td>Inflammation, ACS, UTI</td>
<td>Allergic rejection, delayed graft function, CIN, endotoxemia, cisplatin toxicity, ischemia</td>
</tr>
<tr>
<td>L-FABP</td>
<td>Distal tubule (liver)</td>
<td>NA</td>
<td>4-6, 2-6, NA,</td>
<td>486 ng/mg creatinine</td>
<td>d, S (0.81)</td>
<td>Ischemia, nephrotoxins (cisplatin), idiopathic membranous nephropathy, CKD, sepsis, diabetic nephropathy</td>
<td></td>
</tr>
<tr>
<td>H-FABP</td>
<td>Proximal tubule (heart)</td>
<td></td>
<td></td>
<td></td>
<td>d, S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conventional markers are affected by numerous factors that could impact accuracy. Novel markers appear more accurate because they reflect components of renal tissue, factors that are produced locally or are external factors with constant production.

Abbreviations: d, duration; S, severity; H, HD/RRT; D, death; G, long-term graft loss; CIN, contrast-induced nephropathy; CPB, cardiopulmonary bypass; DGF, delayed graft function; DI, diagnostic; NE, not elevated; NA, not available; NT, not tested; P, plasma; PP, predicts progression; RR, reference range; S, serum; Tx, renal transplant; V, variable; GIT, gastrointestinal tract; ARF, acute renal failure; ACS, acute coronary syndrome; CAD, coronary artery disease; UTI, urinary tract infection; CABVG, coronary artery vein bypass graft.

Data from Devarajan,53 Waikar and Bonventre,54 Edelstein,55 Devarajan,56 Parikh and Devarajan,57 Nickolas et al,58 Coca et al,59 Endre and Westhuyzen,60 Nguyen and Devarajan,61 Oberbauer,62 Ferguson et al,63 Rosner,64 Soni et al,65 and Kronenberg.66

*The times indicated are the earliest time points when biomarker values are increased significantly from baseline (hours).
†Younger than age 40: 90-139 mL/min (males), 80-125 mL/min (females); older than age 40: normal decreases 6.5 mL/min for each decade of life.
‡Lower limit of value that predicts mortality.
§Unpublished data.
possibly diabetes, thyroid dysfunction, high-dose glucocorticoid therapy, and potentially the presence of CV diseases caused Cys-C to deviate higher than expected from GFR, introducing non-GFR variability. Variability with reagents also has been a concern. Values obtained with one reagent were 10% lower within the normal, but 40% higher within a low GFR range when compared with another product. To improve the quality, population-specific Cys-C–based equations and/or a combination of Cys-C– and MDRD-derived values has been proposed but requires further evaluation. Although recognizing this limitation, Cys-C offers complementary prognostic information and may improve GFR estimates in CKD patients. Currently, Cys-C might be a preferable marker for RF in patients with moderately reduced GFR (60-90 mL/min/1.73 m²),74,82,84-90

Assessing Renal Injury

The potential to attenuate or reverse renal injury is far less likely when renal dysfunction is already evident, at least based on current assessment methods. Several promising AKI biomarkers are discussed later.

Neutrophil Gelatinase-Associated Lipocalin

Human neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein initially described to be bound to gelatinase in specific granules of the neutrophil, with recent evidence suggesting physiological activity in the kidney. It is expressed and secreted by immune cells, hepatocytes, and renal tubular cells in various pathologic states. NGAL exerts bacteriostatic effects, which are explained by its ability to capture and deplete siderophores, small iron-binding molecules that are synthesized by certain bacteria as a means of iron acquisition and role in cell survival, inflammation, and matrix degradation.90-95 NGAL gene is up-regulated more than 10-fold in postischemic renal injury in a mouse model and secreted relatively early into the urine. Several recent studies in homogenous (adult and pediatric cardiac surgery),96-103 heterogeneous (intensive care and emergency departments),104-110 CKD,111,112 and other populations113,114 have supported the use of NGAL as an important biomarker in AKI early diagnosis, and prediction of duration and severity of AKI and need for renal replacement therapy (RRT).102,106 NGAL differentiates AKI from changes in GFR owing to chronic disease progression,111 predicts duration of intensive care unit stay,106 and provides prognostic value.122 Specifically, a single urine level of NGAL in the emergency department differentiates AKI from normal function and from prerenal azotemia, and predicts poor inpatient outcome.110

A recent multicenter pooled analysis of published data on 2,322 critically ill children and adults with CRS revealed the surprising finding that approximately 20% of patients display early increases in NGAL concentrations but never develop increases in serum creatinine level. Importantly, this subgroup of NGAL-positive creatinine-negative subjects encountered a substantial increase in adverse clinical outcomes, including mortality, dialysis requirement, intensive care unit stay, and overall hospital stay. Thus, early NGAL measurements can identify patients with subclinical AKI who have an increased risk of adverse outcomes, even in the absence of diagnostic increases in serum creatinine.123

Among acute decompensated HF inpatients, high admission serum NGAL levels were associated with increased risk of worsening RF. In particular, admission NGAL levels of 140 ng/mL or greater had a 7.4-fold increased risk, with a sensitivity and specificity of 86% and 54%, respectively.124 NGAL values are also significantly increased and parallel the clinical severity of CHF, the highest levels among class IV patients. After a 2-year follow-up period, patients with a baseline NGAL level greater than 783 ng/mL had a significantly higher mortality rate. These findings may suggest that NGAL plays a pivotal role in the systemic adaptation to CHF.125 Increased baseline serum levels in acute postmyocardial infarction and CHF correlated with clinical and neurohormonal deterioration and adverse outcomes. In a rat model of postmyocardial infarction HF, NGAL/lipocalin-2 gene expression was increased in the nonischemic left ventricle segments, primarily located to cardiomyocytes. Strong NGAL immunostaining was found within cardiomyocytes of experimental and clinical HF. Furthermore, interleukin (IL)-1â and agonists for Toll-like receptors 2 and 4 were potent inducers of NGAL/lipocalin-2 in isolated neonatal cardiomyocytes, supporting a role of the innate immune system in HF pathogenesis.126 Urinary NGAL also increases in parallel to the New York Heart Association class and also is correlated closely with serum NGAL, Cys-C, SCR, and eGFR.127 This suggests that tubular damage may accompany renal dysfunction in CHF,128 which has prognostic consequences.129

Several issues need to be overcome before widespread clinical use. One concern is the baseline biomarker values for various disease states. Second, NGAL diagnostic performance has varied widely in clinical studies; presently, confounding factors that modify this relationship are unknown. For example, the relationship between urinary NGAL and AKI after cardiac surgery varies with baseline RF, with optimal discriminatory performance in patients with normal preoperative function (baseline eGFR, 90-120 mL/min)102; among orthotopic heart transplant patients, serum NGAL levels were increased significantly among transplant patients but did not significantly correlate with Cys-C or eGFR between transplant patients and controls127; and the predictive value of NGAL increases with grade of AKI.130 Concern still remains over potential confounders. Conditions associated with increased NGAL levels include septic AKI,131 a number of inflammatory and infective conditions,132 and, potentially, cardiac disease.133 Third, in a heterogeneous population, although a single measurement of uNGAL showed moderate predictive utility for AKI and its
severity, its additional contribution to conventional clinical risk predictors appeared limited. Fourth, sensitivity may be limited to certain types of renal injury, particularly ischemic and nephrotoxic injury, and NGAL may not be a specific biomarker for monitoring chronic renal disorders. Lastly, diagnosis appears highly dependent on sampling time, which can be an issue in heterogeneous patients and the asymptomatic nature of renal injury.

Nonetheless, evidence continues to build and NGAL measurement appears to be of diagnostic and prognostic value. In a recent meta-analysis, NGAL levels predicted RRT initiation and in-hospital mortality. Several recent studies showing urinary level response to therapy suggests a future role for NGAL in follow-up evaluation and monitoring the status and treatment of diverse renal diseases reflecting defects in glomerular filtration barrier, proximal tubule reabsorption, and distal nephrons. Thus, the prospects of NGAL as a diagnostic tool, even beyond the realms of nephrology, are exciting but require further clinical research. The commercial availability of standardized clinical platforms for the accurate and rapid measurement of NGAL in urine and plasma will facilitate future investigations as well as direct clinical applications.

IL-18

IL-18 is a proinflammatory cytokine that induces interferon-γ production in T cells and natural killer cells. It is synthesized as a biologically inactive precursor, which requires cleavage into an active molecule by an intracellular cysteine protease similar to IL-1β. IL-18 is both a mediator and biomarker of ischemic AKI. Several early studies showed increases in patients with acute tubular necrosis, prerenal azotemia, nephrotic syndrome, delayed graft function after renal transplantation, chronic renal insufficiency, and urinary tract infections. In contrast nephropathy, cardiopulmonary bypass, critically ill children, and kidney transplantation, urinary IL-18 increases 2 days earlier than SCr. Urine IL-18 increases at 4 to 6 hours after cardiopulmonary bypass, peaks at more than 25-fold at 12 hours, and remains increased up to 48 hours later. IL-18 levels also predict graft function and need for dialysis up to 3 months later. There is also significant evidence that IL-18 contributes to clinical HF and other acute and chronic cardiovascular presentations. Presently, there are no studies of patients with CRS.

Major concerns over IL-18 surround its discriminatory capacity and appropriate use. One concern is a spillover into the urine and its effects as a confounder, differentiating increased cardiac as opposed to renal injury. For example, Haase et al. noted early postoperative urinary IL-18 was not valuable in identifying patients who developed AKI injury but rather it represented a nonspecific marker of cardiopulmonary bypass-associated systemic inflammation. However, because samples were taken preoperatively, immediately postoperative, and at 24 hours, it highlights an ongoing learning curve in biomarker use. In addition, serum IL-18 may be increased in other disease states, for example, autoimmune disorders such as systemic lupus erythematosus, certain leukemias, postoperative sepsis, chronic liver disease, and acute coronary syndromes. On a positive note, serum IL-18 levels were not different between those with and without AKI post-pediatric cardiac surgery and data suggesting its pathophysiological contribution to the renal damage observed during ischemia/reperfusion are positive signs of its discriminatory values and causative effects in renal injury. Thus, IL-18 appears to be a worthwhile addition in a biomarker panel in the assessment of AKI.

Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein that is highly overexpressed in proximal tubule cells after ischemic or nephrotoxic AKI. Several studies have shown KIM-1 in urine and renal biopsy to be increased from predominately ischemic AKI and not from prerenal azotemia, chronic renal disease, and contrast nephropathy. KIM-1 seems to play a role in the pathogenesis of tubular cell damage and repair in experimental and human kidney disease. KIM-1 is a sensitive marker for the presence of tubular damage. It is virtually undetectable in healthy kidney tissue, but tubular KIM-1 expression is strongly induced in acute and chronic kidney disease as well as transplant dysfunction, in which it is associated significantly with tubulointerstitial damage and inflammation. Increased urinary KIM-1 levels are strongly related to tubular KIM-1 expression in experimental and human renal disease, indicating that urinary KIM-1 is a very promising biomarker for the presence of tubulointerstitial pathology and damage. Furthermore, urinary excretion of KIM-1 is an independent predictor of graft loss in renal transplant recipients, showing its prognostic impact. Studies after cardiopulmonary bypass surgery have noted similar findings. KIM-1 also predicts adverse clinical outcomes in various forms of AKI. Data from nondiabetic proteinuric patients suggest that urinary excretion of KIM-1 may have the potential to guide renoprotective intervention therapy. KIM-1 potentially could provide additional prognostic data over eGFR, for tubular damage in CHF. Future studies will reveal whether the sensitive biomarker KIM-1 will become a therapeutic target itself. KIM-1/KIM-1 dipsticks can provide a sensitive and accurate detection of KIM-1, thereby providing a rapid diagnostic assay for kidney damage and facilitating the rapid and early detection of kidney injury in preclinical and clinical studies. The primary limitation of KIM-1 is that time to peak is 12 to 24 hours after insult; thus, it may be of limited use as an early AKI biomarker, however, the ability to detect KIM-1 in urine makes it an attractive option, possibly in a biomarker panel with NGAL and IL-18.
Liver-Type Fatty Acid-Binding Protein

The fatty acid-binding proteins (FABPs) are 15-kDa cytoplasmic proteins. There are 2 types: heart type (H-FABP), located in the distal tubular cells, and liver type (L-FABP), which is expressed in the proximal tubular cells. Both markers have been suggested as useful markers for rapid detection and monitoring of renal injury. H-FABP has been tested as a marker for ischemic injury in donor kidneys. L-FABP has been tested in progressive end-stage renal disease as well as in renal injury after renal transplantation and cardiopulmonary bypass and more recently acute coronary syndromes. In patients undergoing percutaneous coronary intervention (PCI) for unstable angina, urine L-FABP levels were increased significantly after 2 and 4 hours and remained increased for 48 hours. SCr did not change significantly during the study period. Among nondiabetic CKD patients, urine L-FABP levels correlated with urine protein and SCr levels. Notably, L-FABP levels were significantly higher in patients with mild CKD who progressed to more severe disease. Neither SCr nor urine protein differed between those same groups. H-FABP, however, is produced by myocardial damage and its clearance is determined by RF. Furuhashi et al were able to show that the ratio of H-FABP to myoglobin after hemodialysis may be a useful marker for estimating cardiac damage and volume overload in hemodialysis. This may be an advantage of FABP in a panel of biomarkers to discriminate background noise and cases in which troponin levels cannot be interpreted. The main drawbacks are lack of evidence in the HF setting, small sample size of existing studies, and nonavailability of a commercially usable assay. Presently, additional longitudinal studies are needed to show the ability of L-FABP to predict AKI as well as CKD and its progression in cohorts with CKD of multiple etiologies.

Biomarker Panels

Given the complex prerequisites, it is not surprising that no biomarker panel has been sufficiently validated for clinical use. However, based on the differential expression of the biomarkers and heterogeneity of acute decompensated heart failure admission and inability to pinpoint exact time of injury it is also likely that the AKI panels consisting of complementary, sequentially expressed and tandem biomarkers will help distinguish between the various types and etiologies of AKI, and predict clinical outcomes. At present, there have been few studies comparing the use of more than two biomarkers in a panel. Figure 3 highlights how these biomarkers may be used to provide complementary information.

Urinary KIM-1, N-acetyl-β-D-glucosaminidase (NAG), and NGAL were measured at five time points for the first 24 hours after surgery in a prospective study of 90 adults undergoing cardiac surgery. Thirty-six patients developed AKI defined as an increase in Scr of 0.3 mg/dL or greater within 72 hours after surgery. The area under the curve (AUC) for KIM-1 immediately and 3 hours after surgery was 0.68 and 0.65, 0.61 and 0.63 for NAG, and 0.59 and 0.65 for NGAL, respectively. Combining the

![Figure 3](link-to-figure)

**Figure 3.** Chronologic association of SCr and novel biomarkers in predicting renal insufficiency. (A) Time-course of decrease in GFR as compared with increase in SCr. (B) Comparison of traditional late approach versus proposed biomarker early approach in the diagnosis of post-cardiac surgery AKI. Modified from Herget-Rosenthal et al and Hudson et al.
three biomarkers enhanced the sensitivity compared with individual biomarkers: the AUCs for the three biomarkers combined were 0.75 and 0.78. The performance of combining biomarkers was even better among 16 early postoperative AKI patients with AUCs of 0.80 and 0.84, respectively. In a further study of cardiopulmonary bypass, KIM-1, NAG, NGAL, IL-18, Cys-C, and α-1 microglobulin were measured 2 hours after cardiopulmonary bypass, urinary KIM-1 achieved the highest area under the receiver operating characteristic curve (ROC, 0.78), followed by IL-18 and NAG. Only urinary KIM-1 remained independently associated with AKI after adjustment for a preoperative AKI prediction score, or cardiopulmonary bypass perfusion time. In this small pilot cohort, KIM-1 performed best as an early biomarker for AKI. Among diabetic patients undergoing cardiac catheterization there was a significant increase in serum NGAL after 2, 4, and 8 hours, and in urinary NGAL and IL-18 after 4, 8, and 24 hours. Serum Cys-C increased significantly after 8 hours, peaked at 24 hours, and then decreased after 48 hours. L-FABP and KIM-1 increased significantly after 24 and 48 hours. Biomarker panels also have advantages in predicting the need for RRT. Median NGAL and IL-18 levels, but not KIM-1 levels, were moderately accurate, at all time points, in predicting the need for RRT within 1 week, whereas the decrease in SCr was not predictive.

Limitations

Are we there yet? Have we found a renal troponin? Will any single biomarker fully suffice in AKI? Each of these biomarkers have advantages and limitations. The greatest limitation is related to the lack of symptoms. It will be a while yet before we determine if any of these biomarkers will match serum troponin and act as a standalone marker. Although not satisfying all the criteria mentioned earlier, what they do is provide a safety mechanism initially to highlight anticipated risk and additional information on likely renal pathophysiology. A major question is how to set guidelines to order and interpret findings and which biomarkers? We personally believe that one comprehensive renal biomarker is best to address these questions. It ultimately may appear that a panel of biomarkers is required. Candidates for inclusion are NGAL, IL-18, KIM-1, Cys C, and L-FABP. In terms of clinical utility, a reasonable strategy would be addition in conjunction with routine biochemistry, a so-called piggyback strategy, at admission and daily thereafter. Alternatively, selective use when renal injury is anticipated, a strategy that is synonymous with acute coronary syndromes with serial cardiac enzymes (ie, serial renal enzymes). Ultimately, a point of care device would be ideal; some such kits are already in place. It is clear, however, that the learning paradigm is still ongoing. Future studies will need to validate these biomarker panels in a large heterogenous cohort.

Conclusions and the Future of Renal Assessments in CV Patients

Renal dysfunction is an independent and significant contributor to poor heart failure outcomes. Idiosyncrasies in cardio-renal physiology and limitations of conventional diagnostic tools are factors in poor prescription of proven heart failure therapies in these patients. Novel biomarkers of renal injury and function are currently available. These biomarkers also have limitations but they address gaps in information provided from conventional biomarkers (ie, improvements in injury chronology and functional accuracy). Significant limitations in how we use these markers and issues of availability and cost can be addressed only with further exploration. Future research studies should consider addressing these questions.

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