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BIOMARKERS OF HEART FAILURE (WHW TANG, SECTION EDITOR)

Novel Renal Biomarkers to Assess Cardiorenal Syndrome

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Abstract Renal dysfunction (RD) in heart failure portends adverse outcomes and often limits aggressive medical and decongestive therapies. Despite the high prevalence in this population, not all forms of RD are prognostically or mechanistically equivalent: RD can result from irreversible nephron loss secondary to diabetic or hypertensive kidney disease or it can develop secondary to heart failure (HF) itself, i.e., the cardiorenal syndrome. Furthermore, filtration is only one aspect of renal performance such that significant renal impairment secondary to cardiorenal syndrome can exist despite a normal glomerular filtration rate. Renal biomarkers have the potential to inform some of the intricacies involved in accurately assessing cardiorenal interactions. This article discusses novel biomarkers for cardiorenal syndrome and their utility in the prognosis, diagnosis, and targeted treatment of heart failure-induced RD.

Keywords Cardiorenal syndrome · Heart failure · Worsening renal function · Improvement in renal function · Acute kidney injury · Kidney injury biomarkers · Cystatin C · Albuminuria · Neutrophil gelatinase-associated lipocalin · *N*-acetyl-β-D-glucosaminidase · Kidney injury molecule-1 · Interleukin-18 · Blood urea nitrogen to creatinine ratio · Brain natriuretic peptide · C-type natriuretic peptide · Diuretic resistance · Hepatic congestion · Galectin-3

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Introduction

The complex interplay between the heart and the kidney in the setting of concomitant impairment of each organ has been referred to as the cardiorenal syndrome (CRS) [1]. The relevance of the kidney in heart failure (HF) is obvious as it serves as the regulator of fluid and sodium balance in the body. Thus, perturbations in renal physiology are central to the development of volume retention, which is a hallmark of the HF syndrome [2]. Additionally, a requisite to the use of many lifesaving therapies, such as angiotensin-converting enzyme inhibitors, is an adequate renal function. As a result of the above, it is not surprising that it has repeatedly been demonstrated that renal dysfunction (RD) is common in HF and is one of the strongest predictors of morbidity and mortality in these patients [3–6].

Despite widespread recognition of the importance of CRS, progress toward an understanding of this "syndrome" has remained a challenge [7]. The true difficulty lies in the fact that not all elevated creatinine levels in HF occur via the same mechanism [8–10]. Although some patients have RD caused by the HF itself, many patients have comorbid intrinsic kidney disease from shared risk factors such as diabetes or hypertension [11]. Unfortunately, assuming that all RD in HF should be treated similarly is akin to treating all anemia with vitamin B_{12} supplementation and expecting improvement in hemoglobin levels in all patients. It is therefore not surprising in the face of these challenges that the majority of our "cardiorenal" trials have been disappointingly negative [12–16].

However, novel biomarkers provide many opportunities in overcoming these challenges. There are three important purposes for cardiorenal biomarkers: (1) prognostication, (2) discrimination between RD phenotypes, and (3) patient identification for targeted therapeutic intervention. Currently, most cardiorenal biomarkers have aided in the

prognosis, but the ultimate goal is for them to facilitate selection of patients most likely to benefit from specific CRS or HF therapies. The purpose of this review is to provide an overview of biomarkers for CRS highlighting that while in some cases novel means "new," in other cases novel refers to the repurposing of traditional laboratory metrics to inform on CRS. Each biomarker will be discussed in the context of the potential pathophysiology of CRS they may query (Table 1).

Glomerular Filtration and Integrity

Initial recognition of cardiorenal dysfunction focused on the presence of a reduced glomerular filtration rate (GFR). Serum creatinine-based measures of renal function are significantly influenced by a number of factors unrelated to the GFR [17]. Therefore, determining alternative less-biased biomarkers for GFR estimation in addition to parameters that describe glomerular integrity has been the focus of significant research.

Table 1 Novel renal biomarkers and their utility in the prognosis, diagnosis, and targeted treatment of cardiorenal syndrome

Biomarker	Prognosis in CRS	Diagnosis of CRS	Targeted treatment
Glomerular filtration and integrity			
Cystatin C	***	*	None
Albuminuria	***	*	*
Tubular kidney injury			
NGAL	***	*	None
NAG	***	*	None
KIM-1	***	*	None
IL-18	*	*	None
Neurohormonal activation and sodium avidity			
BUN/Cr	***	**	None
Diuretic efficiency	***	**	None
Venous congestion			
BNP	***	**	None
Biochemical evidence of hepatic dysfunction	*	*	None
Tissue fibrosis			
Galectin-3	*	None	None
Mechanism undefined			
CNP	**	None	None

*** Utility strongly demonstrated by evidence, ** utility moderately demonstrated by evidence, * utility only suggested by evidence, *None* no evidence, *NGAL* neutrophil gelatinase-associated lipocalin, *NAG* N-acetyl-β-D-glucosaminidase, *KIM-1* kidney injury molecule-1, *IL-18* interleukin-18, *BUN/Cr* blood urea nitrogen/creatinine ratio, *BNP* brain natriuretic peptide, *CNP* C-type natriuretic peptide

Cystatin C

Cystatin C (CysC) is a 13-kDa cysteine protease, ubiquitous in all nucleated cells that is produced at a constant rate, freely filtered, and not secreted in renal tubules. Despite initial enthusiasm that this marker would perform dramatically better than serum creatinine since it is not primarily determined by muscle mass, frequent discrepancies from measured GFR are now well recognized [18, 19]. Although the data has not necessarily borne out that CysC is vastly superior to creatinine with respect to measured GFR, the sources of bias are different and thus significant, and context-specific incremental information appears to be present with this marker [20••, 21–23].

Prognosis in CRS

The prognostic capability of CysC was first demonstrated in over 4,000 older patients in the Cardiovascular Health Study where CysC was independently and linearly associated with increased cardiovascular (CV) events and mortality, outperforming creatinine [24]. In a subset of patients with chronic HF, the highest quartile of CysC (>1.55 mg/L) was associated with two times the risk of CV mortality adjusted for baseline characteristics [25]. Subsequent larger studies in stable chronic HF confirmed the associated risk of death with increasing CysC even when added to models including estimated GFR (eGFR) using either the Cockcroft-Gault or Modified Diet in Renal Disease (MDRD) equations [21, 26, 27, 28•]. Additionally, elevated CysC identified patients at high risk for death without RD as determined by the MDRD equation [28•]. In patients presenting with acute decompensated heart failure (ADHF), CysC performs similarly as a mortality indicator and is associated with repeat HF hospitalization and adjusted risk of death at 30 days and 1 year, again outperforming eGFR, regardless of the estimating equation used [29–32]. In those patients with eGFR>90 mL/min/1.73 m^2, CysC remained a robust predictor of survival [29]. CysC also aids in risk stratification alongside other powerful HF biomarkers. Lassus et al. demonstrated in 620 HF patients admitted with volume overload that patients with the highest tertile of N-terminal prohormone brain natriuretic peptide (NT-proBNP) and CysC suffered a 48.7 % 1-year mortality compared to 5.2 % in those with the lowest tertile of both markers, while Manzano et al. showed that patients with elevations in cardiac troponin T (>0.011 ng/mL), NT-proBNP (>3.345 pg/mL), and CysC (>1.21 mg/L) had a 66.7 % risk of mortality [29, 32]. Similar additive prognostication of CysC when added to brain natriuretic peptide (BNP) was illustrated in stable HF outpatients [28•].

Diagnosis of CRS

The enhanced value of CysC as a prognostic indicator in HF patients with normal renal function (eGFR>90 mL/min/1.73 m^2) begs the question as to whether CysC is merely more accurately reflecting GFR than creatinine-based measures, particularly in populations with significant muscle wasting. Four out of ten patients without RD presenting with HF have elevated CysC levels indicating that traditional estimates of GFR may underdiagnose RD in HF [26]. To that end, Shilpak and colleagues recently proved the superiority of CysC eGFR across 11 large population studies in 90,750 participants; when CysC eGFR was used resulting in reclassification of patients into different chronic kidney disease (CKD) stages, the relationship between CKD and death was stronger and more linear across all eGFRs [20••]. Furthermore, the increased risk of CV mortality appeared reliably at a CysC-based eGFR<85 mL/min/1.73 m^2. In HF patients, CysC-based eGFR outperformed all other estimating equations with the lowest bias, great precision, and excellent accuracy compared to directly measured GFR using iothalamate clearance [33•]. However, despite potential improved accuracy and risk stratification with CysC, it offers no ability to differentiate different mechanisms for CRS.

Albuminuria

The size- and charge-selective glomerular barrier prevents filtration of the majority of large proteins like albumin and this is in part the reason that albumin is not normally found in the urine [34]. In the setting of glomerular capillary damage, glomerular integrity is disrupted and leakage results in increased amounts of albumin entering the renal tubules producing albuminuria. Additionally, damage to the proximal tubule may inhibit albumin reabsorption mechanisms leading to its appearance in the urine at abnormal levels [35]. Perhaps most commonly associated with diabetes, hypertension (HTN), and both acute kidney injury (AKI) and CKD, albuminuria is a puissant risk factor for both CV death and all-cause mortality, independent of other CV risk factors, and in patients with normal renal function [36, 37]. In chronic HF, microalbuminuria (30–300 mg/g creatinine (Cr)) is present in a third of patients, and macroalbuminuria (>300 mg/g Cr) occurs in 5–11 % of patients [38•, 39, 40]. Although albuminuria is inversely correlated with eGFR and occurs more commonly in HF patients with diabetes, it remains highly prevalent in nondiabetics and those with normal renal function [39]. The mechanism of albuminuria in HF compared to other disease states has not been elucidated. Inflammation and endothelial dysfunction have been proposed as possible etiologies, yet there was no association between markers like C-reactive protein and von Willebrand factor and albuminuria in HF patients [41]. However, correlations between albuminuria and reduced renal blood flow, elevated NT-proBNP levels, and physical exam findings of volume overload have been demonstrated, evoking the potential involvement of "arterial underfilling" and venous congestion [41, 42]. In a study of 115 ADHF patients, in whom spot urine albumin to creatinine ratios (UACR) were measured on days 1 and 7 of hospital admission, the prevalence of microalbuminuria was 42 % and a surprising 31 % of patients had macroalbuminuria [43•]. Interestingly, the mean UACR decreased significantly over 7 days, regardless of changes in renal function, and these improvements in UACR were correlated with similar improvements in NT-proBNP and serum bilirubin [43•]. The improvement in albuminuria alongside the clinical improvement of congestive symptoms of HF exacerbation endorses a role for hypervolemia in the pathophysiology of albuminuria in HF.

Prognosis in CRS

Three substudies of major HF trials have revealed the prognostic power of albuminuria. In 2,310 patients enrolled in CHARM, albuminuria was associated with a 40–80 % increase in the adjusted risk for all-cause mortality, CV mortality, and admission for HF [44]. In the GISSI-HF study, patients with microalbuminuria (hazard ratio (HR)=1.42, 95 % confidence interval (CI) 1.11–1.81, $p=0.005$) and macroalbuminuria (HR=1.70, 95 % CI 1.16–2.50, $p=0.006$) suffered marked increases in mortality, independent of eGFR, diabetes, and HTN [39]. Importantly, in both studies, the magnitude of increased risk associated with albuminuria remained in those patients whose urinary albumin excretion was in the normal range. Baseline proteinuria as assessed by urinary dipstick in over 5,000 patients in Val-HeFT was also independently associated with increased mortality as well as morbid events including sudden death, HF hospitalization, or administration of inotropic agents [42]. This observed risk did not differ between those patients with (58 %) and without baseline RD, implying that proteinuria is either an early precursor of RD or is a result of HF-induced kidney damage via a different mechanism than what leads to reductions in GFR. Still, it is important to remember that patients with significantly decreased eGFR (Cr>2.5 mg/dL) were excluded from this study, so whether existence of more severe RD modifies the survival disadvantage associated with albuminuria is unknown.

Diagnosis of CRS

The prevalence of albuminuria in HF patients without concomitant RD (27 % in CHARM) or diabetes and HTN (36 % in GISSI-HF) suggests that it may be valuable in identifying patients with CRS who would be overlooked using eGFR alone [39, 44]. Examining changes in albuminuria with

decompensation may also further distinguish patients with CRS [43•]. However, although utilizing albuminuria may enhance the sensitivity of CRS discrimination, it also impairs specificity. Until there is a means of determining the etiology of albuminuria in those patients with coexisting diabetes or HTN and HF, albuminuria alone in these patients is unlikely to further phenotype CRS.

Targeted Treatment in CRS

Albuminuria is one of the few cardiorenal biomarkers that has some data related to targeted treatment, albeit not particularly promising. In CHARM, candesartan had no effect on UACR during treatment, nor did aliskerin in the ALOFT trial, but neither trial examined whether patients with albuminuria garnered improved outcomes with additional renin-angiotensin-aldosterone system inhibition despite the lack of changes in UACR [38•, 44]. Still, secondary analyses of clinical trials, while informative, should be interpreted with caution, and currently, there have been no trials of specific CRS therapies directed toward patients with albuminuria in HF.

Tubular Kidney Injury

In the case of AKI, creatinine often lags far behind the incidence of the actual kidney damage. Furthermore, significant kidney damage may exist without meaningful decrements in GFR secondary to renal reserve. Consequently, timely diagnosis of AKI is impeded and alterations in treatment, if appropriate, are delayed. Still, even with earlier recognition of AKI, all worsening in renal function (WRF) in HF is not created equally, a fact supported by the fact that WRF caused by different provocations (i.e., aggressive diuresis or a drop in blood pressure) have dramatically different prognostic implications [45–48]. Newly developed biomarkers of tubular kidney injury, unlike creatinine, have shown promise in earlier AKI identification and offer some discrimination to the site and degree of insult [49]. As a result, the following biomarkers indicative of tubular kidney injury may be of particular importance and utility in CRS.

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25-kDa protein originally found in granules of neutrophils. In steady state, its concentration is less than 20 ng/mL in both the serum and the urine, but it can be elevated in chronic inflammatory conditions. Due to its involvement in iron transport, plasma levels are inversely correlated with indices of anemia [50]. In response to kidney injury, NGAL messenger RNA is transcribed in the kidney, and both serum and urine levels are precipitously increased, peaking within 24–48 h following injury [51, 52]. NGAL is freely filtered in the glomerulus, but it is nearly completely resorbed in the proximal convoluted tubule unless tubular damage exists. Schmidt-Ott outlined a model of NGAL trafficking to highlight the differences in what serum and urine measurements represent: urine NGAL reflects primarily intrarenal production from the thick ascending loop of Henle and collecting ducts, whereas systemic NGAL reflects extrarenal synthesis and potentially some renal-derived NGAL [53].

Urinary NGAL is increased in chronic HF outpatients compared to controls with only minimal correlation with eGFR and no correlation with NT-proBNP [54]. Serum NGAL is also elevated in chronic HF patients, including those with normal renal function [55]. Serum NGAL is not strongly correlated with ejection fraction (EF) or New York Heart Association (NYHA) functional class or with other biomarkers like urinary kidney injury molecule-1 (KIM-1) and *N*-acetyl-β-D-glucosaminidase (NAG) [56, 57]. In patients presenting with ADHF, serum NGAL is significantly correlated with serum creatinine ($r=0.68$, $p<0.0001$) and eGFR ($r=-0.69$, $p<0.0001$), whereas urinary NGAL has little relationship with renal function indices [58]. As a result, some have described serum NGAL as "expensive creatinine."

Prognosis in CRS

In chronic HF, elevated serum and urine NGAL levels were unrelated to all-cause mortality in three smaller single-center studies [56, 57, 59]. However in over 2,000 patients enrolled in the GISSI-HF study, urinary NGAL was weakly associated with increased mortality (adjusted HR=1.23 per SD, 95 % CI 1.07–1.41, $p=0.003$) but failed to demonstrate a significant independent relationship with HF hospitalization [60]. Unlike other injury biomarkers, NGAL has been examined in multiple studies of ADHF and is nearly uniformly associated with increased mortality [55, 61–63]. Aghel et al. showed that an admission serum NGAL≥215 ng/mL was associated with a threefold higher hazard for death, and when admission, systemic levels of NGAL exceed 100 ng/mL in patients with a BNP≥330 pg/mL (the HR for mortality or HF rehospitalization was 16.85, $p<0.006$) [61]. In a secondary analysis of the COACH study, systemic NGAL above the median was associated with increased mortality in patients with RD at discharge (HR=1.97, $p<0.001$) and in those with normal renal function (HR=2.01, $p=0.003$) [55]. NGAL outperformed other renal indices (eGFR and cystatin C) in predicting subsequent mortality. Interestingly, elevated urinary NGAL during admission for ADHF fails to confer an increased risk of death [64•].

Diagnosis of CRS

Some of NGAL's promise as a CRS biomarker lies in its strong associations with the development of WRF in the setting of ADHF regardless of baseline renal function. In one study of ADHF, patients with serum NGAL>140 ng/mL at hospital admission were 7.4 times more likely to develop WRF ($p<0.001$) [61]. Alvelos et al. reported a similar relationship using a cut-off for serum NGAL>170 ng/mL resulting in an area under the curve (AUC) for WRF during admission of 0.93, $p<0.001$ [65]. Serum NGAL remained associated with incident WRF, albeit less powerfully, in a significantly older population (median age=80) admitted with ADHF [66]. Serial measurements of serum NGAL in ADHF also appear to strengthen its ability to predict WRF where the degree of change in NGAL from baseline to peak produced an AUC for WRF of 0.91 compared to admission NGAL alone with an AUC of 0.69 [67]. However, not all study populations have exhibited positive associations between NGAL and WRF; Verbrugge et al. found no relationship between urinary NGAL and WRF or development of persistent renal impairment after discharge [64•]. Although elevated serum NGAL conferred increased risk for WRF in the GISSI-HF study, it lost statistical significance in multivariable analysis [68•].

The differing pathophysiology of renal damage indicated by urinary vs. serum levels of NGAL is unique among tubular injury biomarkers and may ultimately prove vital for characterization of the cardiorenal phenotype [53]. Shrestha et al. evaluated the relationship between both urine and serum NGAL and eGFR, effective diuresis, and natriuresis in 93 patients admitted with ADHF [58]. Serum NGAL was strongly associated with eGFR and predicted the development of WRF yet showed no correlation with metrics of diuresis including weight loss, fluid loss, and natriuresis. Although serum and urine NGAL levels correlated moderately with each other, urinary NGAL demonstrated only weak correlations with eGFR and was unrelated to WRF, and yet elevated levels were associated with decreased diuresis, weight loss, and natriuresis with ADHF treatment. The authors proposed that urinary NGAL may identify HF patients with diuretic resistance, a hallmark of CRS. In a subsequent study from the same group in a less advanced and older ADHF population, urinary levels of NGAL only rose modestly in patients with an increase in serum creatinine, and once urinary NGAL levels were indexed to urine creatinine, the volume of diuresis was identical between groups [69•]. Further research is necessary to understand these findings and to determine whether applying differing treatment strategies based on serum/urinary NGAL profiles translates into clinical benefit [70].

N-Acetyl-β-D-Glucosaminidase

NAG is a large lysosomal enzyme originating in proximal tubule cells and, when detected in the urine, is indicative of proximal tubular injury with disruption of lysosomal integrity [71]. NAG was initially developed and validated as an early accurate marker of subsequent AKI and, when elevated in patients with existing AKI (normal urinary levels are <3 U/g Cr), is associated with dialysis requirement and mortality [72, 73]. In patients with chronic HF, NAG levels are significantly higher compared to healthy controls, a finding that persists after adjustment for baseline eGFR [56]. Furthermore, patients with more significant LV dysfunction (EF<40 %) have greater NAG levels compared to mild dysfunction [57]. Although elevations in NAG are more pronounced in those with HF and concomitant RD, defined as an eGFR<60 mL/min/1.73 m^2, this marker is also elevated in HF patients with preserved renal function [60].

Prognosis in CRS

As a CRS biomarker, NAG provides prognostic value; in multiple HF studies, NAG is associated with increased all-cause mortality and HF hospitalization independent of eGFR [56, 57, 60]. Damman et al. demonstrated in over 2,000 patients participating in the GISSI-HF trial that NAG conferred a significant and independent increased risk for HF hospitalization (adjusted HR=1.17 per SD, $p=0.025$) and mortality (adjusted HR=1.30 per SD, $p=0.001$) in multivariable models. Patients with both RD and high NAG were two times more likely to die compared to those with low NAG and normal renal function [60].

Diagnosis of CRS

Although baseline NAG predicted subsequent WRF in the GISSI-HF trial in a univariate analysis, this relationship dissipated with covariate adjustment [68•]. Interestingly, elevated NAG correlates with congestion as measured by NT-proBNP, BNP, and atrial natriuretic peptide (ANP) and decreases similarly in response to diuretic-induced decongestion [74]. As venous congestion plays an important role in CRS, NAG has potential for phenotyping existing RD in HF. Unfortunately, although elevated urinary NAG is sensitive for tubular injury, it is also increased in diabetes and hypertension as well, limiting its specificity for its ability to differentiate CRS from tubular injury secondary to other etiologies [60].

Kidney Injury Molecule-1

KIM-1 is a type I cell membrane glycoprotein expressed in regenerating proximal tubular cells and facilitates phagocytosis of neighboring apoptotic tubular epithelial cells; it is not expressed in the normal kidney [75]. Within 24 h of tubular injury, KIM-1 increases dramatically (normal<200 ng/g Cr) and sheds its ectodomain which is detectable in the urine [72]. In animal models, elevations correlated with severity of AKI by histopathology, outperforming creatinine and NAG [76]. In HF patients, KIM-1 is only modestly correlated with other biomarkers of tubular injury, eGFR, and urinary albumin excretion [56]. Although levels of KIM-1 are increased in those patients with RD, chronic HF patients exhibit higher levels even in the presence of normal kidney function [60]. Similar to urinary NAG, KIM-1 levels increase as EF decreases and as the severity of HF symptoms increase as exemplified by worse NYHA class [57]. However, in ADHF, Verbrugge et al. noted that KIM-1 levels were only slightly elevated at time of hospital admission [64]. Interestingly, KIM-1 is the only injury biomarker that has also been associated with development of incident HF in the Framingham Heart Study and incident HF hospitalization in the Uppsala Longitudinal Study of Adult Men [77, 78].

Prognosis in CRS

In chronic HF, KIM-1 is associated with increased risk for HF hospitalization and all-cause mortality [56, 57]. In the GISSI-HF study, KIM-1 was also associated with the combined endpoint of HF hospitalization and death (adjusted HR=1.13, p=0.018), but the adjusted relationship lost significance when these endpoints were examined individually [60]. Alternatively, in ADHF, there was no relationship between the levels of KIM-1 on admission and all-cause mortality (HR=1.29, p=0.072) [64•]. Further research is necessary to better understand the prognostic ability of KIM-1 and how/why that differs in chronic versus ADHF.

Diagnosis in CRS

Similar to NAG, KIM-1 is strongly correlated with measures of congestion including NT-proBNP and elevated in patients requiring higher doses of diuretics [57]. The concentration of KIM-1 increases with diuretic withdrawal and subsequently returns to normal with reinstitution of diuretic therapy [74]. Although this pattern was also described for NAG, the rapidity and degree of fluctuations in KIM-1 were significantly more marked than NAG, particularly in those patients with baseline RD. It is important to note that while the levels of KIM-1 were fluctuating, serum creatinine remained relatively unchanged. Increased levels of KIM-1 in chronic HF outpatients is significantly associated with development of WRF over 1 year later when adjusted extensively for baseline characteristics (HR 1.23, 95 % CI 1.09–1.39 per log increase, p<0.001) [68•]. Despite its robust association with WRF in chronic HF, levels of KIM-1 at admission for ADHF did not predict subsequent AKI with treatment nor was it associated with persistent renal impairment following discharge [64•]. The sensitivity of KIM-1 to changes in fluid status and diuretic use coupled with its strong association with WRF in chronic HF suggests that it may be valuable in phenotyping CRS, although the lack of a relationship between KIM-1 and WRF in decompensated HF may in turn limit its utility and therefore deserves further exploration. It is important to note that whether the changes described in tubular function captured with KIM-1 are actually due to HF has yet to be determined.

Interleukin-18

Interleukin-18 (IL-18) is a cytokine that is produced in mononuclear cells, macrophages, and nonimmune cells and, in its active form, mediates inflammation and ischemic injury in multiple organs including the heart, lungs, and colon [49]. In fact, plasma concentrations of IL-18 are elevated in patients with acute coronary syndrome [79]. In the kidney, IL-18 is produced and released from the proximal convoluted tubule within hours of kidney injury, peaking at 12 h and remaining in the system for 48 h [80]. Urinary IL-18 elevations are more specific for ATN than other renal diseases including chronic kidney disease and urinary tract infections [81]. In children undergoing cardiac bypass, increases in IL-18 appeared 6 h prior to the rise in creatinine and improved the AUC for AKI detection from 0.72 to 0.84 [82]. In adults, patients with the highest quartile of urinary IL-18 prior to cardiac bypass experienced significantly increased mortality in those with and without AKI [83]. Interestingly, circulating levels of IL-18 have been reported in patients with HF and in one small study correlated with disease severity [64•, 84, 85].

Prognosis in CRS

In HF, there have been few studies examining IL-18, but Verbrugge et al. examined IL-18 levels in 83 patients admitted with ADHF along with other kidney injury biomarkers. Only IL-18 was significantly associated with all-cause mortality in univariate analysis of this population (HR=1.48, 95 % CI 1.16–1.87, p=0.001) [64•]. Given the strong mortality associations already reported in AKI patients and in patients with coronary artery disease, further investigation into the prognostic potential of this biomarker in CRS is warranted.

Diagnosis of CRS

In ADHF, IL-18 is only modestly correlated with other kidney injury biomarkers and, when corrected for urine creatinine

production, demonstrates no correlation with eGFR or serum cystatin C [64•]. Although IL-18 did not predict WRF during hospitalization, it was the only biomarker significantly associated with persistent renal impairment following discharge; baseline levels>7 pg/g Cr were 68 % sensitive and 60 % specific.

Neurohormonal Activation and Sodium Avidity

HF arises when progressive pump dysfunction can no longer be buffered by endogenous compensatory mechanisms. One of the best studied of these compensatory mechanisms is upregulation of neurohormonal systems such as renin, angiotensin II, aldosterone, vasopressin, and the sympathetic nervous system [2]. In the kidney, the direct effects of neurohormonal activation are analogous to the homeostatic response to acute blood loss, causing a substantial reduction in renal blood flow, GFR, and increased sodium/fluid avidity. In fact, neurohormonal levels have been shown to correlate better with GFR than with left ventricular ejection fraction in HF [4].

Blood Urea Nitrogen to Creatinine Ratio

Although the blood urea nitrogen to creatinine ratio (BUN/Cr) has been widely used clinically to distinguish intrinsic kidney disease from prerenal RD, it has only recently been employed in HF patients with RD, hence its inclusion here as a novel biomarker [86]. Certainly, the individual components of this ratio are well known for their powerful prognostic abilities in HF; however, the BUN/Cr provides additional diagnostic and prognostic value particularly in CRS given what it represents [87]. Renal clearance of urea is determined by the amount filtered and the degree of tubular reabsorption. While decreases in eGFR from any etiology can lead to decreased urea filtration, the tubular reabsorption of urea is largely influenced by neurohormonal activation with increases in angiotensin II and vasopressin leading to higher urea concentration in the proximal tubule and increased urea transporters in the collecting duct, respectively, thereby enhancing absorption [88, 89]. As such, in diseases of increased neurohormonal activation, like HF, the BUN is elevated out of proportion to serum creatinine as opposed to intrinsic kidney disease where filtration may be reduced, but tubular reabsorption of urea is preserved yielding a lower BUN/Cr [90, 91].

Prognosis in CRS

Increasing levels of BUN/Cr are associated with increased mortality in chronic and ADHF despite adjustment for eGFR, but the enhanced value of BUN/Cr lies in its differentiation of high-risk forms of RD in HF [92, 93]. In four separate populations, ranging from stable HF outpatients to severely decompensated inpatients, we have demonstrated that in patients with an elevated BUN/Cr, the adjusted risk of death attributed to RD ranges from 2.2 to 4.6 compared to those with normal renal function, but in patients with a low BUN/Cr, the presence of RD had no impact on mortality (p interaction<0.03 for all; Fig. 1) [5, 94•]. Patients with elevated BUN/Cr also displayed multiple signs of increased neurohormonal activation. These results suggest that the mechanism of eGFR reduction in HF patients (i.e., CRS versus intrinsic kidney disease) is more important than the RD itself.

Diagnosis in CRS

Unlike the irreversible nephron loss associated with intrinsic kidney disease, RD secondary to CRS is often reversible as evidenced by marked improvements in renal function (IRF) in many patients following treatment for ADHF [95, 96]. Our group previously showed in a cohort of 896 patients with ADHF that an admission BUN/Cr≥20 was independently associated with increased incidence of IRF during the hospitalization despite extensive adjustment for baseline characteristics and eGFR (odds ratio (OR)=1.66, 95 % CI 1.15–2.41, p=0.007) [94•]. These results suggest that an elevated BUN/Cr identifies a potentially reversible form of CRS. Further research is required to delineate whether targeted treatment of these high-risk patients yields subsequent benefit.

Diuretic Resistance/Diuretic Efficiency

The failure to realize a significant diuresis or natriuresis following dosing of a loop diuretic signifies a sodium avid state which by in large is driven by neurohormonal activation [97–100]. Importantly, this renal sodium avidity queries a different dimension of renal function than filtration or structural integrity of components of the renal parenchyma. Recently, our group and others have focused on not just the diuretic dose but the *response* to that dose using metrics which attempt to capture the renal response to the diuretic stimulus: (1) diuretic efficiency defined as net fluid output in milliliter per 40 mg furosemide equivalents, (2) weight change in kilogram per 40 mg furosemide equivalents, and (3) natriuretic response to continuous IV furosemide defined as urine sodium to urine furosemide ratio (U_{Na}:$U_{Furosemide}$) [101•, 102, 103•].

Prognosis in CRS

In two separate cohorts, we demonstrated that while diuretic efficiency was only modestly correlated with diuretic dose, net

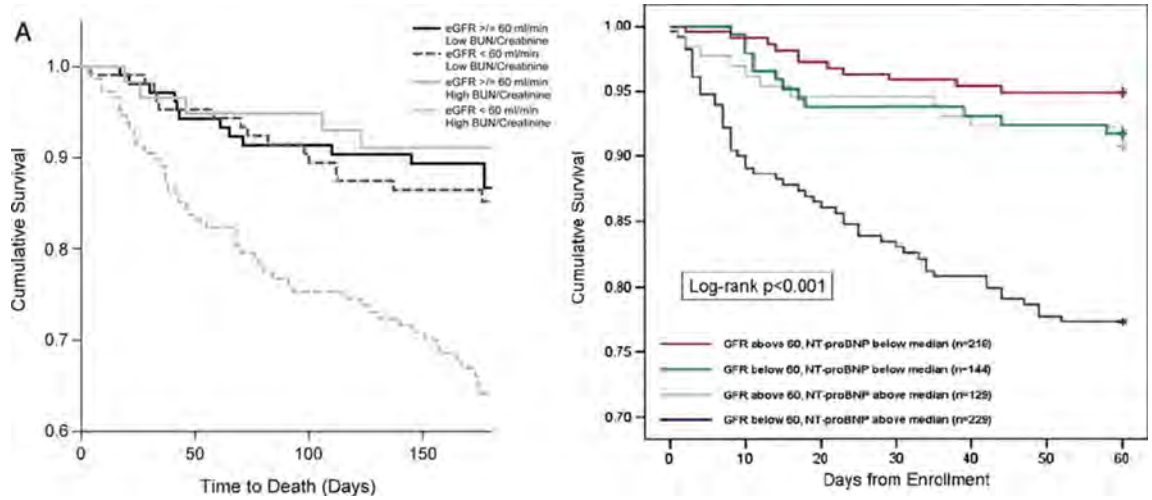

Fig. 1 Survival of heart failure patients as a function of GFR and BUN/Cr (*left panel*) and GFR and NT-proBNP (*right panel*) in two clinical trial populations of decompensated heart failure. Patients with renal dysfunction (estimated glomerular filtration rate less than 60 mL/min/1.73 m^2) and elevated BUN/Cr or NT-proBNP are at the highest risk for mortality. Evaluation of markers of congestion (NT-proBNP) or neurohormonal activation (BUN/Cr) in heart failure patients with renal dysfunction may aid in distinguishing CRS from other forms of renal impairment. *Left panel* reproduced from Testani et al. [5], with permission from John Wiley & Sons. *Right panel* reproduced from van Kimmenade et al. [136], with permission from Elsevier

urine output, and estimated GFR, it was independently associated with significantly increased mortality; patients with diuretic efficiency below the median in the ESCAPE trial experienced nearly three times the risk of death compared to those patients with diuretic efficiency above the median despite extensive adjustment for baseline and in-hospital characteristics including net fluid output and diuretic dose (HR= 2.86, 95 % CI 1.53–5.36, p=0.001) [101•]. Furthermore, the relationship between low diuretic efficiency and increased mortality was present in both patients on low- and high dose diuretics reinforcing that diuretic efficiency captures more than just the diuretic dose. Valente et al. found similar results where patients with less weight loss per 40 mg furosemide equivalents experienced an increased hazard for 60-day HF rehospitalization and 180-day mortality [102]. A final metric of diuretic responsiveness, the U_{Na}:$U_{Furosemide}$ was examined by Singh et al. who measured spot urine sodium, creatinine, and furosemide in 52 ADHF patients hospitalized on continuous IV furosemide infusion [103•]. U_{Na}:$U_{Furosemide}$ was not significantly associated with eGFR or diuretic dose but higher U_{Na}:$U_{Furosemide}$ was associated with 3.6 times the likelihood of increased urinary output and 2.7 times the likelihood of increased weight loss in 24 h. Patients with U_{Na}:$U_{Furosemide}$< 2 mmol/mg (indicative of low diuretic efficiency) experienced less weight loss and fluid removal in the first 24 h and were at significantly increased risk for death, HF rehospitalization, and cardiac transplantation in an analysis adjusted for age and eGFR (HR=2.2, 95 % CI 1.08–4.49, p=0.032). The results of the aforementioned studies suggest that metrics of diuretic responsiveness are superior to diuretic dose in identifying HF patients with diuretic resistance who in turn are at increased risk for poor outcomes.

Diagnosis in CRS

Diuretic resistance or low DE in HF is believed to result from a number of different mechanisms. First, a significant reduction in GFR can decrease drug delivery to the tubules, but as most loop diuretics are bound to albumin and secreted by the proximal tubular cells, adequate drug delivery is far more dependent on renal blood flow than filtration [97]. Diuretics themselves can lead to increases in activation of RAAS subsequently decreasing renal blood flow and tubular secretion [104]. Other mechanisms of resistance that have been proposed are pharmacodynamic like diuretic "braking" during which acute tolerance develops as means to preserve intravascular volume and hypertrophy of distal tubular cells in response to increased sodium delivery downstream induced by diuretics leading to increased sodium reabsorption and decreased responsiveness even in the setting of normal drug delivery [98]. Due to the fact that most of the proposed mechanisms for diuretic resistance are independent of GFR yet indicative of HF-induced RD, accurate assessment of diuretic resistance may identify patients with significant cardiorenal dysfunction. As an example, we found that the presence of a low eGFR did not exclude the possibility of excellent DE and vice versa [101•]. Furthermore, patients with U_{Na}:$U_{Furosemide}$<2 mmol/mg in the study by Singh et al. were also more likely to experience WRF with treatment, a hallmark of CRS [103•]. Further research is necessary to explore these metrics of decreased diuretic responsiveness and whether targeted treatment strategies in these patients are beneficial.

Venous Congestion

One of the chief mechanisms believed to be involved in cardiorenal dysfunction is systemic venous congestion. Data from animal models illustrates how increases in renal vein pressures yield decreased renal blood flow, GFR, and sodium excretion, abnormalities which improve with relief of congestion [105]. Furthermore, positive associations between volume overload and RD in HF patients have only strengthened the potential role of venous congestion in CRS [95, 106]. The inherently complicated interplay between venous congestion and CRS is not the focus of this review; however, those biomarkers which represent or result from congestion may prove extremely useful in deciphering the pathophysiology of CRS while simultaneously aiding in its recognition [107].

Brain Natriuretic Peptide

BNP is a hormone produced by the myocardium in response to increased wall stretch and elevated filling pressures. Both BNP and its biologically inactive form, NT-proBNP, are elevated in HF and are well established as diagnostic and prognostic indicators [108, 109]. Increases in NT-proBNP during hospitalization for ADHF are associated with a threefold increase in mortality [110]. Similarly, increases in BNP in stable HF patients over 4 months also predict poor prognosis [111].

Prognosis in CRS

Possibly due to the common misconception that elevations of BNP and NT-proBNP in patients with RD merely reflect a reduction in eGFR, their use in patients with HF and RD was not extensively explored prior to a study by van Kimmenade and colleagues. In 720 patients presenting with ADHF, both RD (eGFR<60 mL/min/1.73 m^2) and NT-proBNP above the median (>4,647 pg/mL) were independently associated with mortality; however, those patients with both RD and elevated NT-proBNP suffered the worst mortality (OR=3.46, 95 % CI 2.3–5.6, $p<0.001$). In fact, patients with RD but lower NT-proBNP levels had a similar prognosis to patients with normal renal function suggesting that NT-proBNP may characterize RD in HF instead of simply reflecting it (Fig. 1) [112].

Diagnosis of CRS

In the aforementioned study, van Kimmenade et al. also examined the relationship between WRF (rise in creatinine >0.3 mg/dL) and NT-proBNP during treatment of ADHF [112]. Notably, WRF was in fact associated with decreased 60-day survival, but this survival disadvantage was restricted to those patients with an elevated NT-proBNP. Patients with WRF in the setting of lower NT-proBNP had similar survival to those patients with stable renal function. As WRF in HF is heterogeneous, utilization of NT-proBNP in addition to WRF may further distinguish CRS from other forms of RD in HF.

Biochemical Evidence of Hepatic Dysfunction

Physicians have long been aware of the negative impact of HF on the liver: reduced hepatic perfusion can lead to hepatocellular injury with increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while elevated venous pressure and congestion ultimately result in centrilobular necrosis with increases in bilirubin (BIL) and the international normalized ratio (INR) [113–115]. Notably, similar pathophysiologic mechanisms like venous congestion and reduced perfusion are thought to contribute to CRS. As both the kidneys and the liver occupy the same circulatory and congestive environment, congestion and abnormal cardiac output secondary to HF likely affect both organs similarly and simultaneously. Therefore, laboratory evidence of hepatic dysfunction (i.e., congestive hepatopathy) may identify patients with concomitant CRS.

Prognosis in CRS

Multiple studies have demonstrated that elevated liver function tests in patients with acute and chronic HF, specifically AST, ALT, and bilirubin, are associated with increased mortality and HF rehospitalization, but only bilirubin has retained prognostic ability in adjusted analyses [115, 116, 117•, 118]. Still, whether markers of liver dysfunction are of heightened prognostic value in patients with RD has yet to be explored.

Diagnosis in CRS

Similar to CRS, the centrilobular necrosis signified by elevated liver function tests and characteristic of HF-induced liver dysfunction is reversible with decongestion [113]. Therefore, patients presenting with ADHF and markers of hepatic congestion may also be more likely to experience IRF with return to compensation. We previously demonstrated in a cohort of 823 patients admitted with ADHF that those who presented with elevated AST, ALT, BIL, or INR (in those not on warfarin) were significantly more likely to experience IRF (defined as a ≥20 % improvement in eGFR) during the hospitalization, suggesting the presence of CRS at the time of presentation [119•]. The strength of the associations between markers of liver dysfunction and subsequent IRF was much stronger in patients who presented with marked RD (eGFR≤45 mL/min/1.73 m^2). Patients with RD and an elevated BIL at admission were five times more likely to experience IRF (OR=5.1, $p<0.001$), while in patients without RD, an elevated admission BIL was not significantly related to IRF (OR=1.6, $p=0.06$, p interaction=0.01). Similar results were observed for an

elevated admission INR and ALT. In the absence of clear-cut diagnostic criteria for CRS, using evidence of HF-induced dysfunction of another organ to inform on the likely presence of concomitant CRS deserves further investigation.

Tissue Fibrosis

Renal tissue fibrosis can develop secondary to various modes of kidney injury both acute and chronic, while myocardial fibrosis is a sine qua non of the HF syndrome and cardiac remodeling. As tissue fibrosis is involved in the final common pathway for damage to both organs, biomarkers along these pathways may improve our understanding about the cross-talk between the heart and kidneys in CRS.

Galectin-3

Galectin-3 is a β-galactoside-binding lectin, expressed both intracellularly and extracellularly, where it is involved in cell proliferation, apoptosis, inflammation, and cell growth. In the kidney, the role of galectin-3 appears to be protective in AKI, attenuating fibrosis, yet also activates kidney fibrosis in the setting of persistent renal injury [120, 121]. In the myocardium, galectin-3 has binding sites on cardiac fibroblasts and induces their proliferation and ultimately collagen deposition leading to ventricular dysfunction and myocardial fibrosis [122]. Galectin-3 is measured in the blood with levels ≥17.8 ng/mL considered elevated according to the package insert.

Patients with both chronic and decompensated HF demonstrate similarly increased galectin-3 levels, as do patients with both reduced and preserved EF; there is no correlation between galectin-3 and metrics of disease severity including NYHA functional class [112, 123–125]. Although galectin-3 was helpful in diagnosing suspected acute HF, its performance was inferior in comparison to NT-proBNP as a diagnostic biomarker [112].

Prognosis in CRS

There is a strong relationship between galectin-3 and increased mortality in both stable chronic and decompensated HF patients. In the PRIDE substudy, ADHF patients with elevated admission galectin-3 had ten times the odds of death in 60 days after adjustment for eGFR and baseline characteristics, and Lok et al. reported an adjusted HR of 1.24 for galectin-3 in an outpatient HF cohort of 240 patients [112, 124]. When measured at discharge following a HF exacerbation, galectin-3 has also recently been shown to predict 30-, 60-, 90-, and 120-day risk for HF rehospitalization, significantly improving patient reclassification in readmission models [126•]. Fluctuations in galectin-3 are also significantly associated with survival [127]. In a secondary analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA, HF outpatients) and COACH (ADHF patients) trials, patients whose galectin-3 levels increased by >15 % over 3–6 months had a significantly increased adjusted risk for all-cause mortality and HF hospitalization (CORONA HR=1.54, $p<0.001$; COACH HR=2.04, $p=0.026$) [128•]. Although all the aforementioned studies adjusted their comparisons for renal function, whether RD modifies the relationship between galectin-3 and mortality in HF has yet to be examined. However, Tang et al. reported in a single-center study that the magnitude of the survival disadvantage attributed to increased galectin-3 was more marked in HF patients with concomitant elevations in serum CysC compared to those with normal CysC ($p<0.001$) [125]. Further research is required to delineate the prognostic value of galectin-3 in CRS.

Diagnosis of CRS

Given the powerful mortality associations reported for galectin-3 in HF, one implication is that it may serve as a surrogate for kidney function. However, as galectin-3 is predominantly hepatically cleared and is only modestly correlated with eGFR, this is less likely. Furthermore, in over 2,000 subjects in the Framingham Offspring Study, patients with normal renal function (mean eGFR~90 mL/min/1.73 m^2) and baseline galectin-3 in the highest quartile were at significantly increased odds of developing incident RD defined as an eGFR<60 mL/min/1.73 m^2 (adjusted OR=1.47, 95 % CI 1.27–1.71, $p<0.0001$) [129]. Therefore, galectin-3 elevations in this cohort were not merely reflecting abnormal filtration. Despite the strong correlations between galectin-3 with incident RD, to date, there are no studies investigating an association between galectin-3 and WRF in HF, leaving its potential to distinguish HF-induced RD unexplored.

Undefined Mechanism

C-Type Natriuretic Peptide

C-type natriuretic peptide (CNP) is a member of the natriuretic peptide family which, similar to BNP, results from cleavage of a precursor and subsequent postprocessing that yields the mature, active form, CNP22. Although CNP has been detected in cardiac tissue, it is predominantly a vascular endothelial product with vasodilatory properties that indirectly lead to decreased cardiac filling pressures [130]. Unlike BNP and ANP, CNP has much less of a diuretic effect and a very brief circulatory half-life, potentially limiting its use as a biomarker in the serum. However, CNP is also produced and processed

in the kidney and is detectable in the urine, offering a different method in which measuring CNP may prove beneficial [131]. Given that the stimulation for CNP release in the kidney in heart failure is not completely understood, CNP's potential role as a CRS biomarker is described here without a specific CRS mechanistic context.

In symptomatic HF patients, plasma concentrations of both CNP and NT-proCNP are significantly elevated compared to controls and are associated with HF disease severity expressed by NYHA functional class and EF [132]. Interestingly, CNP levels are also increased in patients with asymptomatic LV dysfunction [133]. Although elevations of NT-proCNP increased the accuracy diagnosing HF above BNP alone, it was not superior as a diagnostic tool [134].

Prognosis in CRS

Given that CNP is also produced by the renal tubules and correlated with serum creatinine, elevated urinary levels of CNP and NT-proCNP may indicate both renal tubular damage and congestion thereby providing unique prognostic information in CRS over natriuretic peptides or other tubular injury markers alone. In a study of 58 ADHF patients, Zakeri et al. demonstrated that urinary NT-proCNP was independently associated with all-cause rehospitalization and death and outperformed both KIM-1 and NGAL as mortality predictors [135•]. Serum CNP was also elevated in patients with ADHF but was not correlated with urinary forms of CNP and showed no association with mortality or rehospitalization.

Diagnosis of CRS

Although all isoforms of CNP are elevated in the serum and urine of ADHF patients, it has not been studied specifically in HF patients with RD. Urinary CNP may in fact serve as a partial marker of tubular injury, but until it is further explored in normal patients and patients with other forms of RD, its capacity to distinguish CRS is unknown.

Conclusions

As described in this review, there is a growing literature of promising and novel biomarkers for cardiorenal dysfunction. Although the focus of this research thus far has centered on prognostication, the currently available and emerging biomarkers in this area query a diverse spectrum of mechanistic pathways and biology. As a result, it is likely that through continued research in this area, pathways to differentiate specific mechanism for renal dysfunction ultimately allowing patient-specific therapeutic approaches will be possible.

Compliance with Ethics Guidelines

Conflict of Interest Meredith A. Brisco and Jeffrey M. Testani declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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