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Biomarkers in kidney and heart disease

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Abstract

There is much symptomatic similarity between acute kidney disease and acute heart disease. Both may present with shortness of breath and chest discomfort, and thus it is not surprising that biomarkers of acute myocardial and renal disease often coexist in many physicians' diagnostic work-up schedules. In this review we explore the similarities and differences between current and future tests of myocardial and renal injury and function, with particular emphasis on the diagnostic utility of currently available biomarkers to assist with the diagnosis of cardiorenal syndromes. Imaging studies have not traditionally been viewed as clinical biomarkers, but as tests of structure and function; they contribute to the diagnostic process, and we believe that they should be considered alongside more traditional biomarkers such as blood and urine measurements of circulating proteins and metabolites. We discuss the place of natriuretic peptides, novel tests of kidney damage as well as kidney function and conclude with a discussion of their place in guiding future research studies whose goals must include better characterization of the degree of dysfunction imposed on one organ system by failure of the other.

Keywords: acute kidney injury; cardiorenal syndromes; chronic kidney disease; decompensated heart failure

Introduction

Over the last decade, multiple biomarkers have been identified as potential contributors for cardiorenal disease. Epidemiological data have demonstrated a close relationship between cardiorenal disease and clinical outcome (Figure 1). This leads to the issue whether assessment of cardiorenal biomarkers will improve the ability to predict (i) who is at risk for cardiorenal disease, (ii) who is at risk over and above the predictive value of established biomarkers/risk factors and finally, (iii) who will gain substantial improvement through elimination of these cardiorenal risk

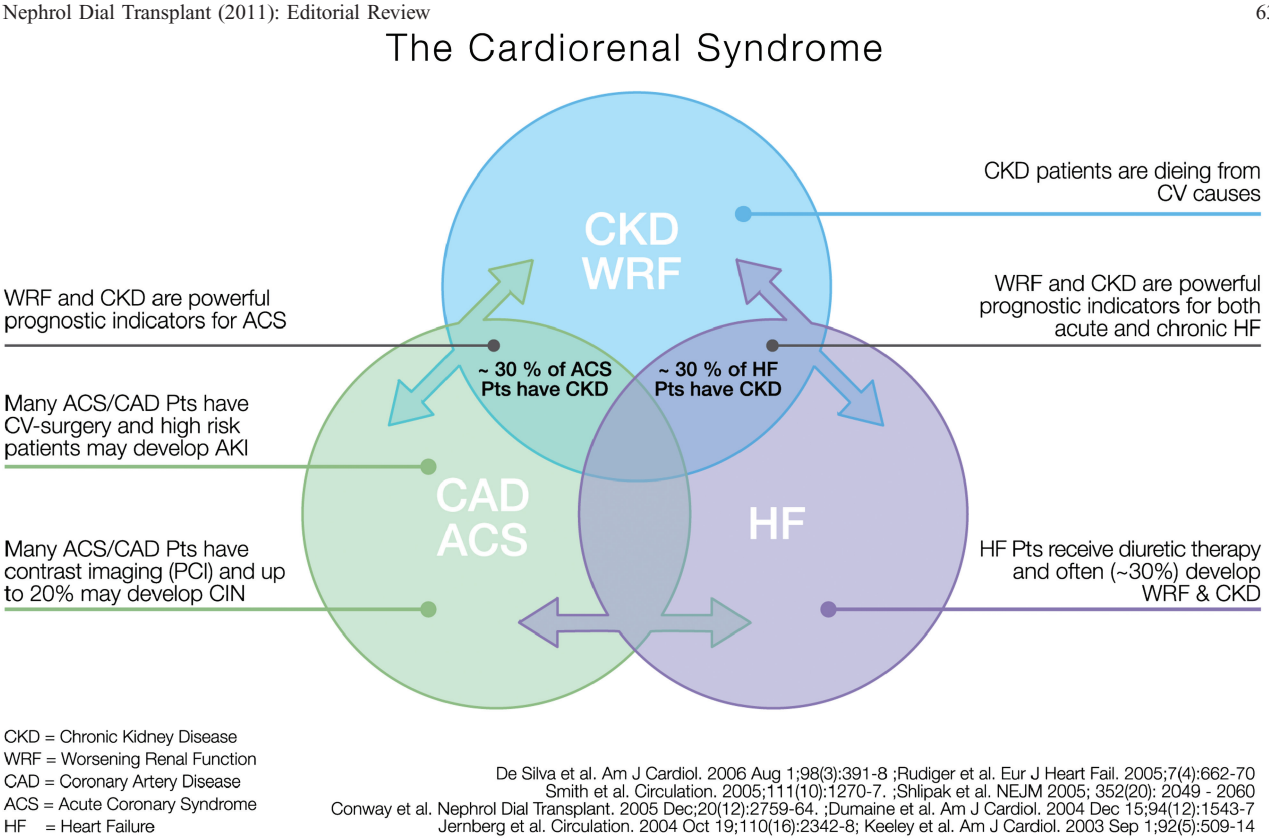

Fig. 1. The cardiorenal syndrome.

indicators. Biomarker levels should change in parallel with the degree of organ injury even in the absence of typical clinical signs and should enable early intervention. Furthermore, the level of an ideal biomarker should correlate with both prognosis and response to treatment. Finally, the ideal biomarker should be sensitive (an early sign of organ injury) and specific (typical of the organ damage). Measurement should be technically easy with good reproducibility.

We discuss classical and novel concepts and biomarkers of causal interactions between the kidney and the heart in various stages of cardiorenal disease. Integration is essential as there is tremendous overlap between patients with coronary disease (CAD), heart failure (HF) and renal dysfunction.

The intention is to integrate quantitative assessment of biomarkers into the diagnosis of the various cardiorenal syndromes (CRS), especially those that deal with acute renal injury on top of acute cardiac disease. If biomarkers are to be clinically useful in these settings, physicians must be able to answer the following questions: (i) can biomarkers be used to (early) identify and classify CRS? (ii) Can biomarkers be used to risk-stratify patients with regard to ultimate reversibility of the syndrome in question? (iii) Can biomarkers be used as targets for treatment? (iv) Can biomarkers be used to monitor the effects of treatment? (v) Can imaging of the heart and kidneys be combined effectively with biomarkers across the spectrum of diagnosis and treatment of CRS?

It is clear that this manuscript cannot answer all of these questions at the present time. What will be explored, however, will be how currently available biomarkers might fit into the new definition of CRS, where the gaps are in our knowledge of biomarkers in CRS [especially those involved in acute kidney injury (AKI)], and finally, what types of studies are needed to demonstrate the presumed clinical value of biomarkers in CRS.

What is a CRS?

A large proportion of patients admitted to the hospital have various degrees of heart and kidney dysfunction [1]. Primary disorders of one of these two organs often result in secondary dysfunction or injury to the other [2,3]. These interactions represent the pathophysiological basis for a clinical syndrome. Although conventionally defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to HF [4], the term CRS is also used to describe the negative effects of reduced renal function on the heart and circulation (more appropriately named renocardiac syndrome). However, older definitions of CRS have been challenged recently as advances in the basic and clinical sciences have changed our understanding of organ crosstalk and interactions. Of interest is that some therapies may have efficacy in the prevention and treatment of both cardiac and renal injury [5–7]. Recently, a new definition has been proposed [8] which focuses on

the complexity of the interrelationship of heart and kidney, including an emphasis on which organ is the initiator of functional damage and which organ is indirectly affected.

To address the inherent complexity of cardiorenal functional deficits and to stress the bi-directional nature of these heart–kidney interactions, the new classification of the CRS includes five subtypes whose terminology reflects their primary and secondary pathology, time frame and simultaneous cardiac and renal dysfunction (Figure 2).

The CRS can thus be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other. Type I CRS reflects an abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive HF) leading to AKI. Type II CRS describes chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive chronic kidney disease. Type III CRS consists of an abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing an acute cardiac disorder (e.g. HF, arrhythmia, ischaemia). Type IV CRS describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events. Type V CRS (not represented in Figure 2) reflects a systemic condition (e.g. sepsis) simultaneously causing both cardiac and renal dysfunction. With both acute and chronic HF the resultant kidney dysfunction is often of a potentially reversible, pre-renal variety without structure damage and thus can be reversed with successful therapy, cardiac transplantation and left ventricular assist device.

It is postulated that a number of cardiorenal biomarkers may potentially help to characterize these subtypes of CRS and suggest the timing of treatment initiation and its likely effectiveness. While the current data are too premature to test this hypothesis for all types of CRS, the identification of patients and the pathophysiological mechanisms underlying each CRS subtype may help physicians understand the clinical derangements, provide the rationale for management strategies and allow the design of future clinical trials with more accurate selection and stratification of the population under investigation.

Biomarkers for HF—the ever-expanding role of natriuretic peptides

B-type natriuretic peptide measurements (BNP and NT-proBNP) are now established tools for the diagnosis of acute decompensated HF [9] and represent independent predictors of cardiovascular events and overall mortality in clinical settings spanning critical illness [10] to stable HF [11]. NPs are elevated in patients with CRS in which AKI occurs as a consequence of AHF, whether new or decompensated. Moreover, NPs have shown prognostic utility in patients with various stages of renal insufficiency [12,13]. End-diastolic cardiac myocyte stretch leads to pro-

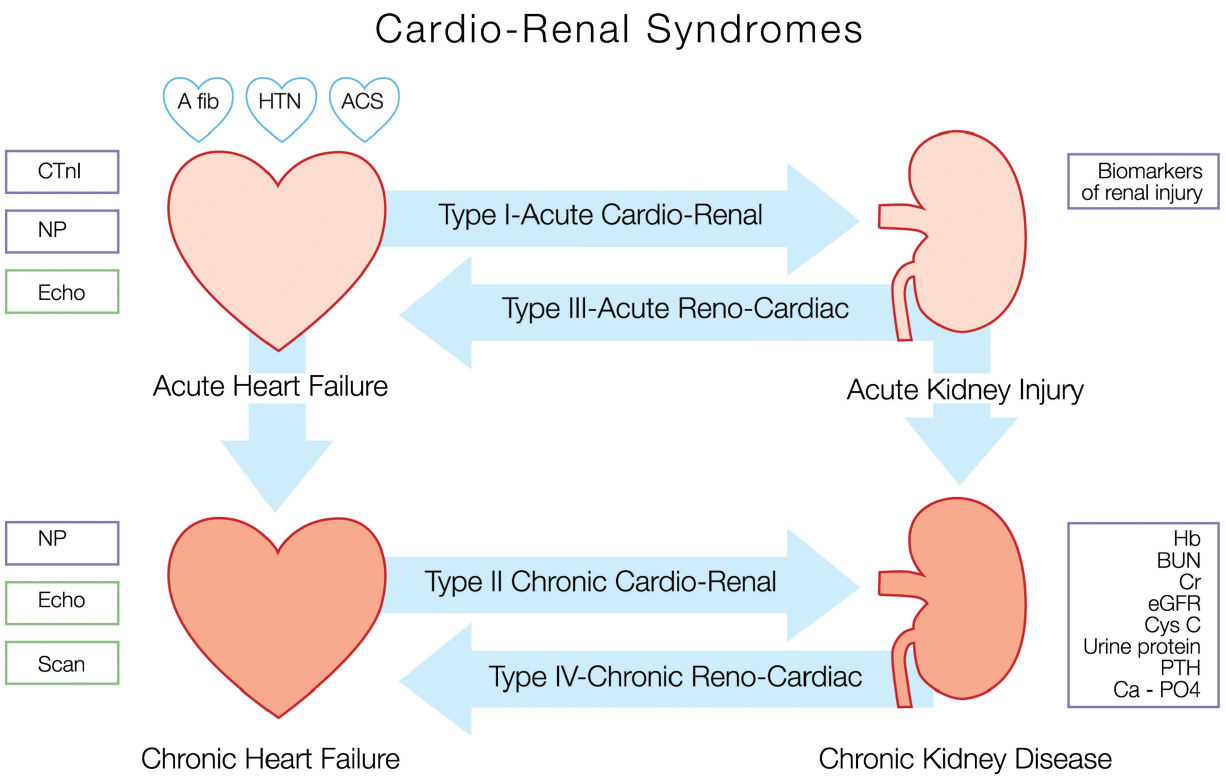

Fig. 2. Biomarkers that are currently used in various cardiorenal syndromes. Acute coronary syndrome (ACS), atrial fibrillation (A fib), blood urea nitrogen (BUN), calcium (Ca), creatinine (Cr), cystatin C (Cys C), estimated glomerular filtration rate (eGFR), haemoglobin (Hb), hypertension (HTN), natriuretic peptides (NP), parathyroid hormone (PTH), phosphate (PO4).

duction of BNP, with vasodilatory and natriuretic properties [14]. Recent evidence suggests that, in HF, there is both a resistance to the actions of BNP [15] and a deficiency of the active form of BNP [16]. BNP mediates its effects via binding to a specific receptor, which in turn causes production of cyclic guanosine monophosphate (cGMP), leading to normal biological effects of BNP. Cyclic GMP is in turn degraded by phosphodiesterases (PDE), such as PDE5. In an experimental model of HF, Forfia and Liang and colleagues were able to mimic the haemodynamic effects of BNP by inhibiting PDE5 with sildenafil, but only in failing canine hearts, implying that HF may represent a state of natriuretic peptide desensitization [15]. Liang and colleagues were able to show significantly increased amounts of proBNP (the biologically inactive precursor of active BNP) in the plasma of advanced HF patients. The inability of certain diagnostic tests to clearly distinguish between various—active and inactive—forms of circulating B-type natriuretic peptides suggests a situation in which hormonal activity is low in relation to plasma levels [16]. Nevertheless, there is an association of elevated BNP with accelerated progression of non-diabetic chronic kidney disease to end-stage kidney disease [17].

The relationship between NPs and renal function

Although many previous studies support the usefulness of BNP in the diagnosis and management of HF patients [18,19], the relationship between BNP, renal function and the severity of HF is less clear. It is well established that patients with chronic kidney disease have higher levels of both BNP and NT-proBNP than age- and gender-matched subjects without reduced renal function, even in the absence of clinical HF [20]. While these higher serum levels of natriuretic peptides have been attributed to reduced renal clearance, there is likely some contribution from increased myocardial wall stress due to hypertension, ventricular hypertrophy, subclinical ischaemia or cardiac remodelling/myocardial fibrosis [21,22]. Although renal clearance is currently regarded as its main mechanism, the exact mechanism remains to be elucidated [23,24]. Only few studies explored the renal handling of proBNP-derived peptides. In healthy individuals, renal extraction ratios between 0.15 and 0.20 were reported for both BNP and NT-proBNP, and similar values were found in patients with CHF, liver cirrhosis and in subjects with hypertension. For this reason, cut-points for NPs for the detection of acute HF have to be adjusted in patients with chronic kidney disease, especially in those with an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/m^2 [25–30]. The Breathing Not Properly trial evaluated the diagnostic performance of a point-of-care BNP assay in the diagnosis of HF in patients presenting to the emergency department with dyspnoea and eGFR ≥ 15 mL/min/m^2 (Figure 3) [23].

In those patients with an eGFR <60 mL/min/m^2 and in whom dyspnoea was not related to HF, mean BNP values were up to nearly 300 pg/mL, approximately 3-fold higher than the accepted cut-off point of 100 pg/mL proposed to diagnose HF. These data corroborate the observations of Forfia *et al.* [24] who reported that despite similar haemodynamic overload, those patients with an eGFR ≤ 60 mL/min/1.73 m^2 had 4-fold higher plasma or aortic BNP levels versus those with a GFR >60 mL/min/1.73 m^2. This study also demonstrated that up to 63% of patients with BNP levels between 100 and 250 pg/mL and varying degrees of renal insufficiency did not have a final diagnosis of HF. In order to maintain optimal diagnostic performance, the authors recommended to increase the cut-point for detecting HF to 200 pg/mL when eGFR is <60 mL/min/m^2.

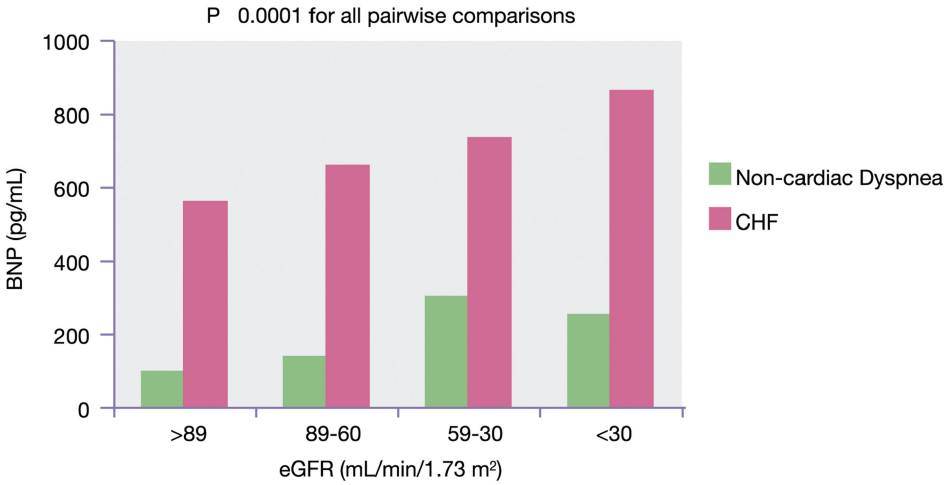

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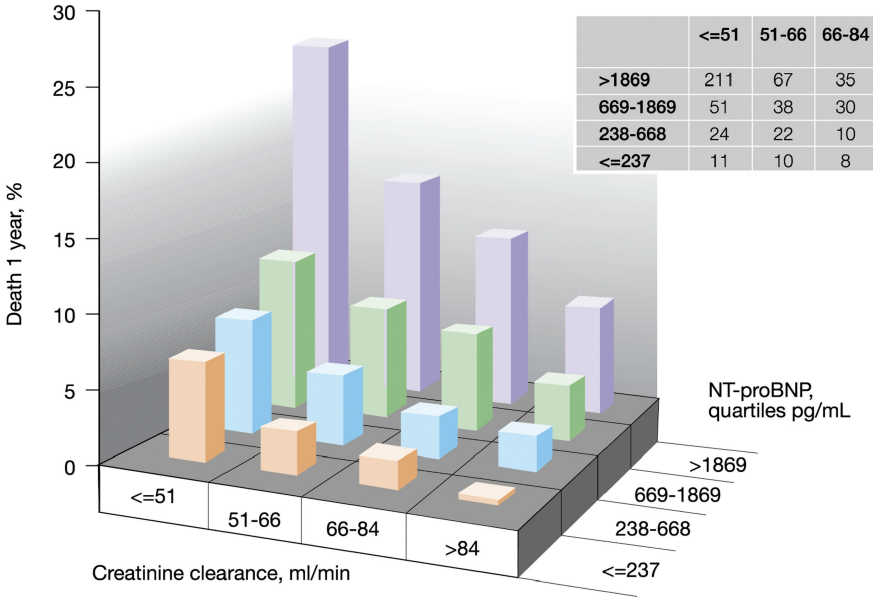
Fig. 3. Mean BNP as it relates to GFR.



	<=51	51-66	66-84	>84
>1869	211	67	35	14
669-1869	51	38	30	11
238-668	24	22	10	9
<=237	11	10	8	2

Fig. 4. Mortality at 1-year follow-up among strata of patients, according to quartiles of NT-proBNP and quartiles of creatinine clearance.

Similar findings were reported for NT-proBNP. In the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study [18], Januzzi and colleagues used NT-proBNP in the evaluation of dyspnoea in patients presenting to a single centre urban emergency department. With a cut-point set at 300 pg/mL for excluding acute HF, they reported a negative predictive value of 94 and 100% for patients with a GFR < and ≥60 mL/min/1.73 m^2, respectively. In contrast to the exclusion cut-points, the optimal NT-proBNP cut-points for identifying CHF appeared to be age dependent: <450 pg/mL for subjects <50 years of age, 900 pg/mL for subjects ≥50 but <75 years of age and 1200 pg/mL for patients ≥75 years. Since renal function deteriorates with age, one might speculate that these different cut-points reflect, to some degree, age-dependent deterioration of renal function. Their data demonstrated good sensitivity and specificity (85 and 88%, respectively) of the aforementioned cut-off values in subjects with an eGFR ≥60 mL/min/1.73 m^2. However, in patients with a GFR <60 mL/min/1.73 m^2, there was a drop in specificity to 68%. In an effort to improve the specificity in these patients, the cut-point was adjusted based upon the receiver-operating characteristic (ROC) curves to a single age-independent value of 1200 pg/mL for patients with an eGFR <60 mL/min/1.73 m^2. When this cut-off criterion was applied, sensitivity remained similar (89%) and specificity improved to 72%. Finally, in patients with severe renal insufficiency (eGFR <44 mL/min/1.73 m^2), this cut-point of 1200 pg/mL appeared to be sensitive and specific enough to diagnose HF (92% sensitivity and 70% specificity). Januzzi also showed that the combination of NTpro BNP levels and creatinine clearance is highly prognostic in acute HF (Figure 4). In summary, BNP, which is only mildly affected by renal function, is likely to be more specific than NT-proBNP in detecting cardiac dysfunction in the presence of renal diseases. NT-proBNP, with reduced renal clearance, may be more appropriate to detect renal dysfunction when cardiac dysfunction is already present.

Other cardiac biomarkers

Cardiac troponins have been identified as biomarkers for ischaemic myocardial injury, while BNP is typical of HF, and myeloperoxidase is a potential sign of oxidative and inflammatory damage [31].

Cardiac troponins are excellent risk predictors in this setting [30]. Markers such as these are sensitive and specific and correlate with the severity of injury, even in the absence of typical clinical features [32]. Although an association of elevated cardiac troponins with inferior outcome for renal patients has been demonstrated to display prognostic value for CRS types III and IV, the specificity and sensitivity of cardiac troponins for diagnosing acute CAD in patients with renal dysfunction are points of concern. Moderate elevations of cardiac troponins are common in clinically stable chronic renal failure patients without significant myocardial damage. Up to 73% of patients on chronic haemodialysis have cTnT above the normal range [31,32]. Increased levels of troponin from cardiac myocytes in patients without evidence of overt coronary heart disease could be explained by structural alterations of the cardiac muscle during uraemia. Furthermore, patients with renal failure also commonly have HF, and severe HF is known to be associated with elevated serum troponins in the absence of clinical myocardial ischaemia or infarction [33–36]. There is encouraging evidence for the prominent role of pro-inflammatory cytokines in chronic HF. The overproduction and release of pro-inflammatory cytokines, particularly tumour necrosis factor-alpha, interleukin (IL)-1 and IL-6, have been shown to exert an effect on ongoing myocardial cell injury [37–39]. However, due to the non-specific na-

ture of many of these cytokines as well as difficulty in measurement, they are not routinely used in the clinical arena.

Not only can biomarkers contribute to an early diagnosis of acute heart injury or failure but they can also help in the prediction of outcomes in chronic diseases. In CRS types II and IV, adverse cardiovascular outcomes are clinically associated with plasma levels of specific biomarkers [39–41]. Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein (CRP), serum amyloid A protein and ischaemia-modified albumin are among markers which have been demonstrated to correlate with outcome in CKD patients [42–44].

As with the case of CRP, it has been suggested that this hepatic-derived protein is not only a biomarker but also a mediator of vascular disease, which directly inhibits endothelial progenitor cell differentiation, survival and function [45]. As these cells represent key components of angiogenesis and vascular response to ischaemia, this observation provides a mechanistic link between chronic inflammation and atherosclerosis, a finding very relevant to the haemodialysis population.

AKI

While cardiac markers, particularly the NPs, have been found to be valuable for HF, Figure 1 demonstrates a gap when it comes to markers of AKI. AKI may be the primary event that leads to cardiac dysfunction (type III CRS), or AKI can result from acute cardiac dysfunction (type I CRS). AKI is a condition with an increasing incidence in hospital and ICU patients. Using the recent RIFLE consensus definitions and its Injury and Failure categories, AKI has been identified in close to 9% of hospital patients [46,47] and, in a large ICU database, AKI was observed in more than 35% of critically ill patients [48]. It is not only associated with increased morbidity and mortality on the short and long term but also with increased healthcare costs [49,50]. AKI can affect the heart through several pathways (delineated in Figure 5) whose hierarchy is not well established.

Pathophysiology

AKI can result from decreased renal blood flow, a toxic insult to the renal tubule, tubulo-interstitial inflammation or a

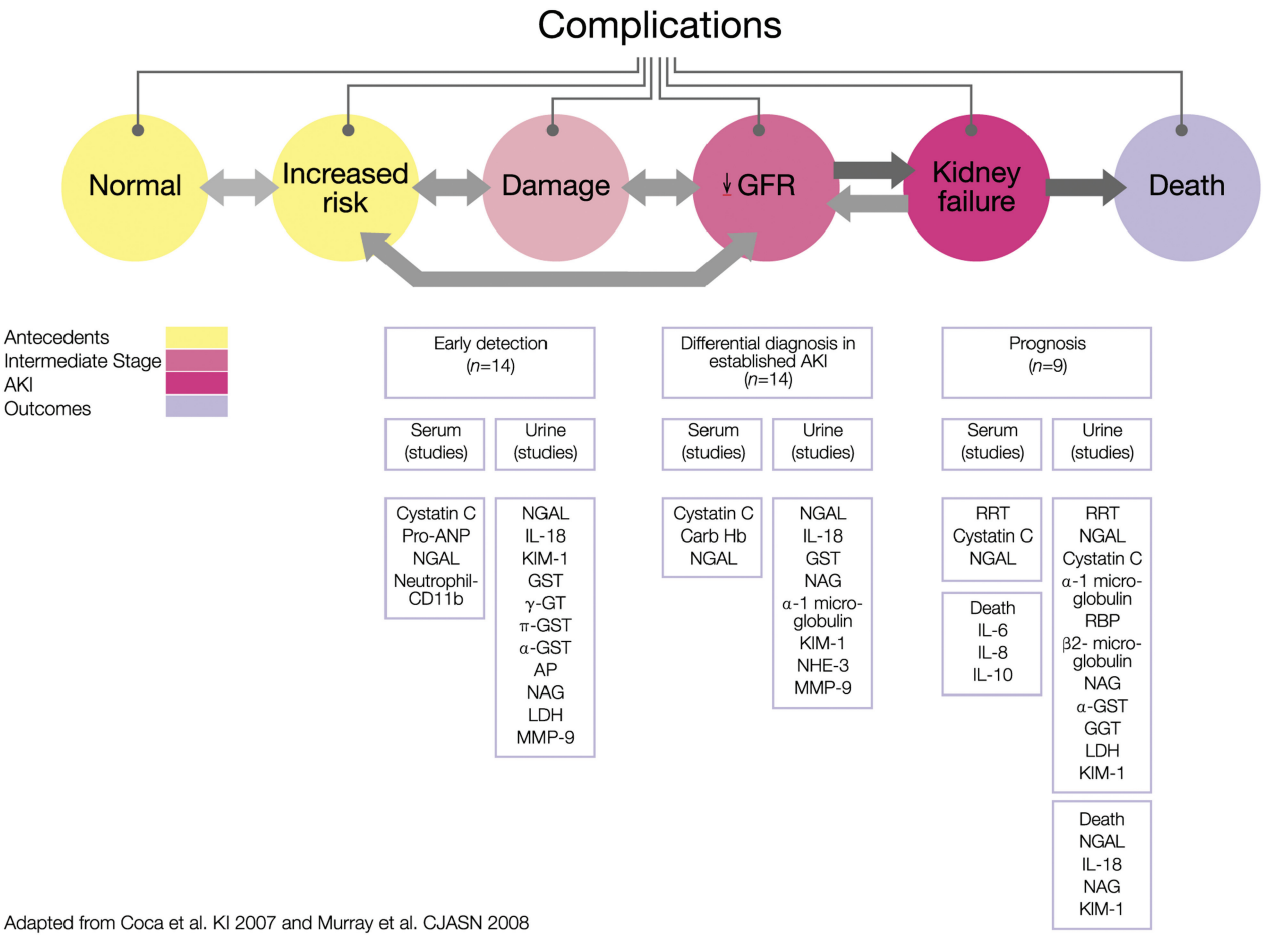


Fig. 5. Acute kidney injury (AKI), blood urea nitrogen (BUN), fatty acid binding protein (FABP), glomerular filtration rate (GFR), glutamyl transpeptidase (GT), glutathione-s-transferase (GST), interleukin (IL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), matrix metalloproteinase 9 (MMP-9), *N*-acetyl-β-D-glucosaminidase (NAG), natriuretic peptides (NP), neutrophil gelatinase-associated lipocalin (NGAL), renal replacement therapy (RRT), retinoid binding protein (RBP), sodium hydrogen exchanger (NHE).

primary reduction in GFR. Our understanding of the pathogenesis of human AKI is characterized by the lack of histopathologic information. This lack of information stems from the risks associated with renal biopsy (especially repeated renal biopsy), which make it ethically unjustifiable to obtain tissue from patients who do not have suspected parenchymal disorders such as vasculitis or primary glomerulonephritis. In the absence of such information, we have to rely on indirect assessments, such as blood and urine tests. To overcome such limitations, animal models of AKI have been developed which enable state-of-the-art measurements to be made. Pathophysiologic mechanisms contributing to AKI following the initial insult include vasoconstriction, desquamation of tubular cells, intraluminal tubular obstruction resulting in tubular back leak and local production of inflammatory mediators resulting in interstitial inflammation, small vessel obstruction and local ischaemia.

Serum creatinine, which has traditionally been used in almost all definitions of AKI, is a suboptimal marker following injury, when levels are often not truly reflective of GFR. In the setting of AKI, the delay between changes in serum creatinine and changes in GFR inhibits the ability to accurately estimate timing and severity of injury. Thus, there is an urgent need to find biomarkers that will permit an early diagnosis of AKI and possibly be used to risk-stratify patients and follow their course of treatment.

There appears to be an opportunity to refine the diagnosis and management of CRS in light of the recent discovery of novel AKI biomarkers. For instance, using cDNA microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury has recently been discovered [48,51,52]. An ideal biomarker of AKI should identify the primary location of injury (proximal tubule, distal tubule, interstitium or vasculature), address the duration of kidney failure (AKI, chronic kidney disease or 'acute-on-chronic'), discern the AKI subtype (pre-renal, intrinsic renal or post-renal), identify the aetiology (ischaemia, toxins, sepsis or a combination), differentiate AKI from other forms of acute kidney disease (urinary tract infection, glomerulonephritis or interstitial nephritis), stratify risk and estimate prognosis (duration and severity of AKI, need for renal replacement therapy, length of hospital stay, and mortality), define the course of AKI and allow the monitoring of response to interventions.

In CRS type I, the early diagnosis of AKI remains a challenge [53]. This is also true in CRS type III, where AKI is believed to be the primary factor leading to cardiac dysfunction. In both cases, classic markers such as creatinine increase when AKI is already established, and, accordingly, with this late indication of the injury, very little can be done to prevent it or to protect the kidney [54,55].

Biomarkers of renal injury

Neutrophil gelatinase-associated lipocalin

Human neutrophil gelatinase-associated lipocalin (NGAL) was originally identified as a 25-kDa protein covalently bound to gelatinase from neutrophils. NGAL is normally expressed at very low levels in several human tissues, including kidney, lungs, stomach and colon. NGAL expression is markedly induced in injured epithelia and is elevated in the serum of patients with acute bacterial infections [56]. NGAL seems to be one of the earliest markers in the kidney after ischaemic or nephrotoxic injury in animal models, and it may be detected in the blood and urine of humans soon after AKI [57–61]. Several studies have confirmed these findings; in intensive care adult patients with AKI secondary to sepsis, ischaemia or nephrotoxins, NGAL is significantly increased in the plasma and urine when compared to normal controls [62]. Human kidney biopsies in these settings demonstrate intense accumulation of immuno-reactive NGAL in 50% of the cortical tubules. In children undergoing cardiopulmonary bypass, NGAL was increased significantly in plasma and urine 2–6 h after surgery in those patients who subsequently developed AKI; the rise in creatinine was seen only 48–72 h later. In this setting, both urine and plasma NGAL were powerful independent predictors of AKI, with an outstanding area under the curve (AUC) of 0.998 for 2-h urine NGAL levels and 0.91 for 2-h plasma NGAL measurement [63]. Similar findings have been reported in adults who develop AKI after cardiac surgery, with NGAL elevation occurring 1–3 h after surgery [64].

NGAL has also been evaluated as a biomarker of delayed graft function in kidney transplantation [65]. The AUC for the ROC curve for prediction of delayed graft function based on urine NGAL at day 0 was 0.9, indicative of an excellent predictive capacity [66]. In other settings, urine NGAL predicts the severity of AKI and dialysis requirement in children [67], while elevated plasma and urine NGAL levels also predict AKI caused by contrast media [68–70] and AKI in critically ill patients admitted to intensive care [71].

In a recent study, 635 patients were admitted to hospital with either AKI, pre-renal azotaemia, chronic kidney disease or normal kidney function. A single measurement of urinary NGAL was able to differentiate those with AKI from other categories, with sensitivity and specificity of 90 and 99%, respectively. Additionally, urinary NGAL was highly predictive of clinical outcome [72]. A note of caution in the interpretation of NGAL values is that they may potentially be influenced by a number of coexisting variables such as pre-existing renal disease and systemic or urinary tract infections [73].

Cystatin C

Cystatin C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule and not secreted into the urine. Its blood levels are not affected by age, gender, race or muscle mass; thus, it appears to be a better predictor of glomerular function than serum creatinine in patients with CKD. In AKI, urinary excretion of cystatin C has been shown to predict the requirement for renal replacement therapy earlier than creatinine [74]. In the intensive care setting, a 50% increase in serum cy-

statin C predicted AKI 1–2 days before the rise in serum creatinine, with an AUC–ROC of 0.97 and 0.82, respectively [75]. Serum cystatin C has been compared to NGAL in cardiac surgery-mediated AKI [76]. Both biomarkers predicted AKI at 12 h, but NGAL outperformed cystatin C at earlier time points. Consideration of them together may allow a better appreciation of the extent of both structural and functional damage of the kidney.

Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a protein detectable in the urine after ischaemic or nephrotoxic insults to proximal tubular cells [77–79]. Urinary KIM-1 seems to be highly specific for ischaemic AKI and not for pre-renal azotaemia, CKD or contrast-induced nephropathy [80]. In response to AKI, the KIM-1 ectodomain is cleaved and detectable in urine, where it is otherwise undetectable. The extent of tubulo-interstitial damage and fibrosis has been associated with urinary KIM-1 concentrations, and KIM-1 mRNA levels correlate strongly with urinary KIM-1 concentration in rats exposed to bilateral renal ischaemia [79]. KIM-1 has been shown to be predictive of AKI in adults and children undergoing cardiopulmonary bypass in a time frame between 2 and 24 h post-surgery. KIM-1 seems to represent an interesting additional marker for AKI, adding specificity to the high sensitivity displayed by NGAL in the early phases of AKI.

N-acetyl-β-D-glucosaminidase

N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal brush border enzyme found in proximal tubular cells. It is relatively big (>130 kDa) and is therefore not filtered through the glomerular membrane [78–80]. NAG has been shown to function as a marker of kidney injury, reflecting particularly the degree of tubular damage [80]. It is not only found in elevated urinary concentrations in acute and chronic kidney disease but also in diabetic patients, patients with essential hypertension and HF [83–86]. In selected patient populations, patients with higher NAG levels do not only suffer more frequently from acute renal dysfunction but also more often experience albuminuria and more severe structural renal damage [87]. In patients with acute renal failure, urinary NAG independently predicted the occurrence of hospital death or need for dialysis [80]. In primary glomerulonephritis, urinary NAG levels were significant predictors of functional outcome [81,82].

Interleukin-18

Interleukin-18 (IL-18) is a pro-inflammatory cytokine detected in the urine after acute ischaemic proximal tubular damage [88]. It displays sensitivity and specificity for ischaemic AKI with an AUC >90% [89] with increased levels 48 h prior to increase of serum creatinine [90]. Urinary NGAL and IL-18 have been studied as tandem biomarkers for delayed graft function following kidney transplantation [66].

In conclusion, NGAL, serum cystatin C and IL-18 appear to perform best for the early diagnosis of AKI. Serum cystatin C, urine IL-18 and urine KIM-1 appear to perform best for the differential diagnosis of established AKI. Urine NAG, KIM-1 and IL-18 appear to perform best for the risk prediction after AKI. Other biomarkers have been studied and represent an interesting and promising contribution to future diagnostic approaches to AKI and progression of CKD.

Future biomarkers for CRS

Figure 6 delineates the CRS paradigm with potential future cardiac and renal markers. While it is beyond the scope of this paper to delineate each of these potential markers, several excellent reviews are available [91–97].

Imaging

Imaging techniques have an additional role with respect to laboratory biomarkers in CRS (Figure 7).

They may enhance, extend and refine our ability to quantify renal damage and function. Traditionally, kidney damage has been diagnosed and measured using biochemical measurements, although it is likely that as we enter the age of molecular and functional imaging this will change such that imaging techniques will truly justify the label 'biomarker'.

No specific imaging test to diagnose CRS is currently available. However, the usual imaging techniques for diagnosis and follow-up of cardiac and renal diseases may be applied with these general rules:

In patients affected by suspected CRS, it is prudent to avoid the use of iodinated contrast media if not strictly necessary.

The presence of CAD should be excluded by stress echo or stress myocardial perfusion (SPECT/PET) in types III, IV and V CRS and in types I and II CRS when the primary cardiac disease is valvular, congenital or myopathic.

Additional information about the aetiology and the severity of kidney injury in selected patients can be obtained using ultrasound scans and morpho-functional examinations.

A role may be expected in the future for MR techniques, both in heart and kidney evaluation, but at the present time MR appears not appropriate for routine application, except in selected cases of HF.

In the future, research should be directed toward experimental studies that apply molecular imaging techniques (MRI and MRS, PET etc.) to the search for in vivo specific markers for diagnosis and severity evaluation of the different types of CRS (Figure 8).

Also in the future, non-invasive imaging techniques should be refined to quantitate renal blood flow. Such data can then be correlated with cardiac and renal biomarkers and most importantly guide ongoing therapy designed to optimize renal blood flow and ultimately preserve kidney function.

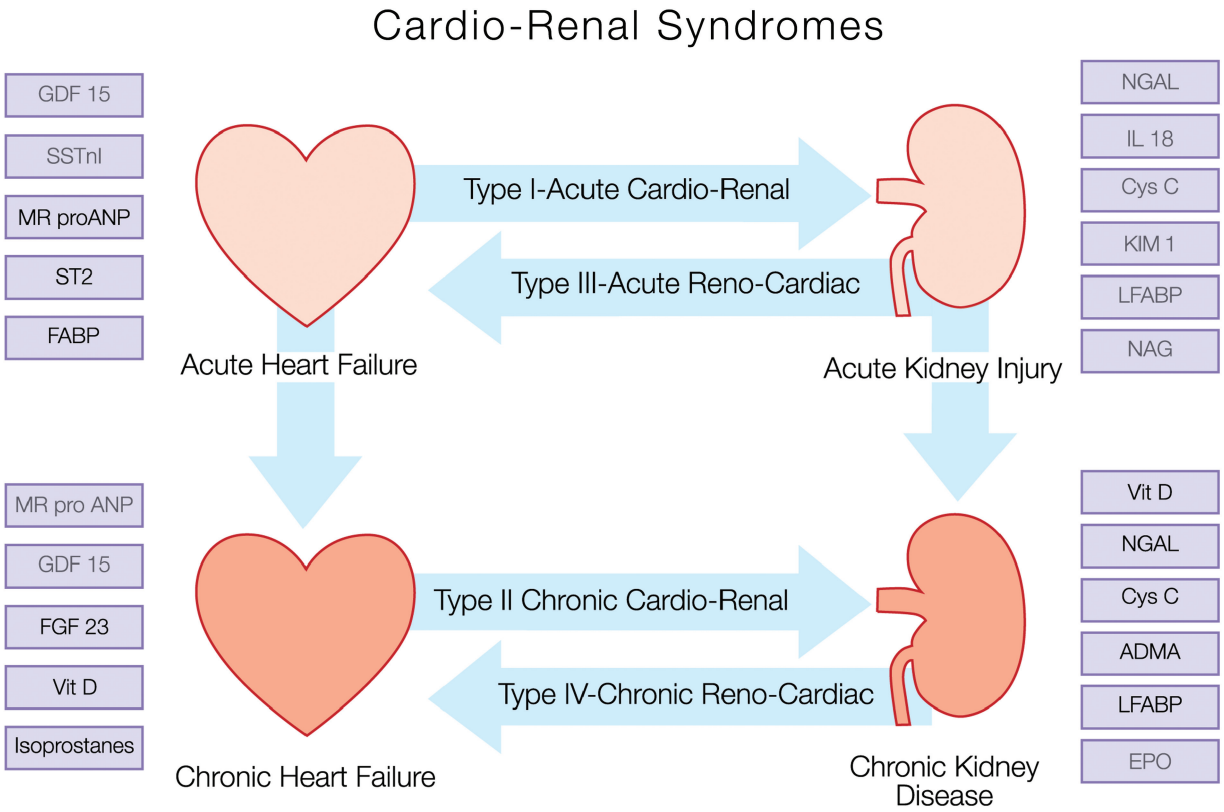


Fig. 6. Cystatin C (Cys C), erythropoietin (EPO), fatty acid binding protein (FABP), interleukin (IL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), *N*-acetyl-β-D-glucosaminidase (NAG), natriuretic peptides (NP).

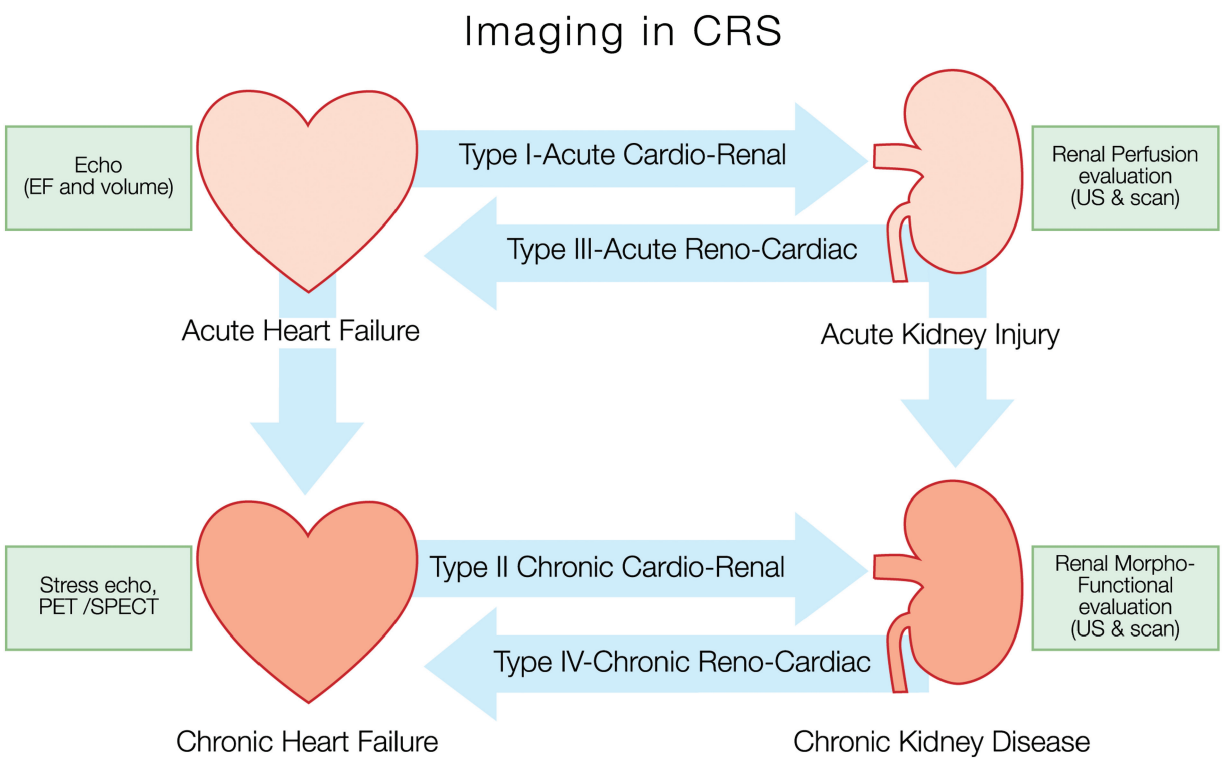


Fig. 7. Imaging in cardiorenal syndromes.

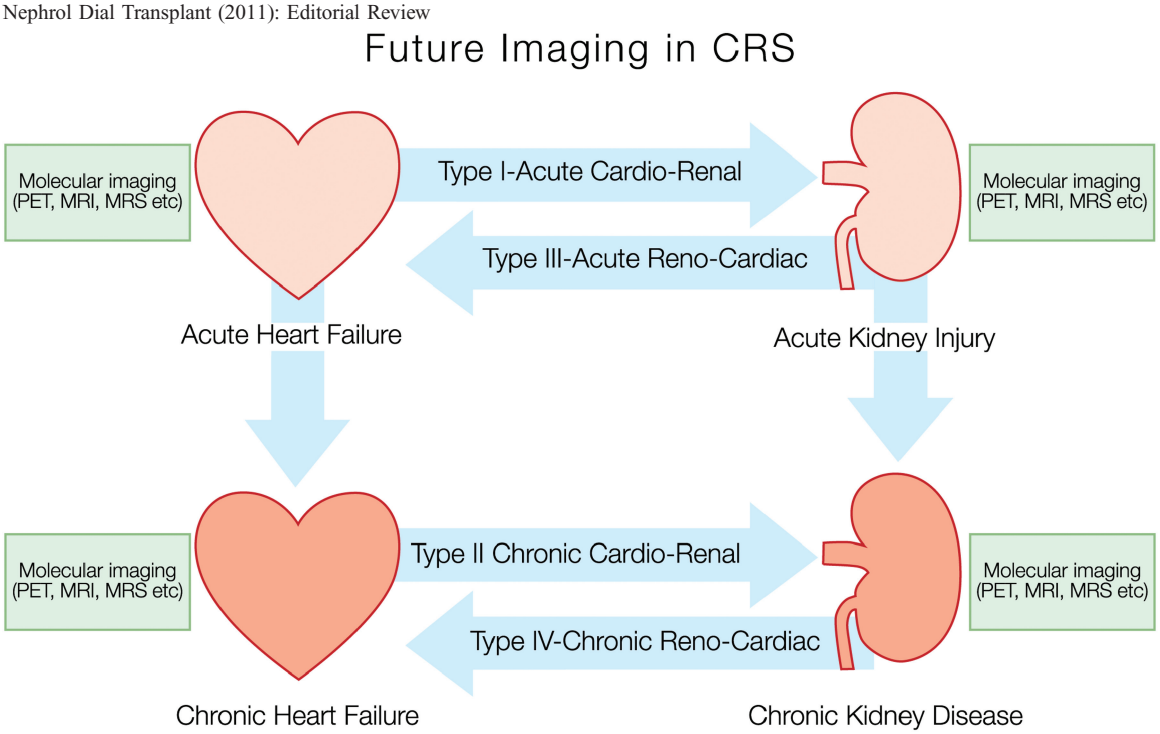


Fig. 8. Future imaging in cardiorenal syndromes.

Future studies

In order to determine the true value of biomarkers in CRS, many studies will need to be performed. Below is an outline of potentially important areas of investigation with several specific trials recommended.

A. Studies to address novel biomarkers of AKI

Determine if it is necessary to redefine CRS by tubular or glomerular biomarkers of AKI.

Ascertain the time course during injury as well as the response to recovery.

Explore differences in various AKI markers in diseases like sepsis, ARDS, contrast media, etc.

Determine what markers are complementary.

Determine how these markers will add to the natriuretic peptides.

Determine the additive value of biomarkers with imaging.

B. Studies that explore specific cardiorenal diseases

Acute coronary syndrome (ACS)—what is the role of early markers of AKI of ACS in terms of prognosis and treatment?

ACS—can a rapidly rising biomarker of renal injury following diagnostic angiography predict renal dysfunction?

CABG—trials of renal prevention drugs such as BNP, ANP and arginine vasopressin antagonists could be carried out in patients undergoing CABG or immediately following CABG targeting AKI biomarkers such as NGAL.

CHF—determine if the acute CHF patient seen in the ED with a spike in NGAL 2 h after receiving diuretics is at high risk for the development of worsening renal dysfunction or not.

CHF hospitalization—does a small increase in NGAL in someone whose BNP level has tapered off during diuresis represent a reduction in circulating volume to slightly below euvolaemia?

CHF hospitalizaton—can the safety of ACE/ARB/spironolactone therapy inititiation in hospital be monitored by early AKI biomarkers?

CHF outpatient—can AKI biomarkers be used to titrate ACE inhibitor therapy when baseline renal function is diminished?

CHF outpatient—BNP levels are beginning to be used to predict decompensation in stable patients with HF (Figure 9). Will adding a renal biomarker of either acute or chronic injury give additive value?

Conclusions

Recent innovative research studies have identified and characterized several novel biomarkers for HF and AKI. These advances will hopefully herald an advance in the understanding, diagnosis and treatment of CRS. It is anticipated that these biomarkers may be used to make an earlier diagnosis of CRS and identify the specific type of CRS in question. It is also anticipated that biomarkers will allow risk stratification with regard to reversibility and will pro-

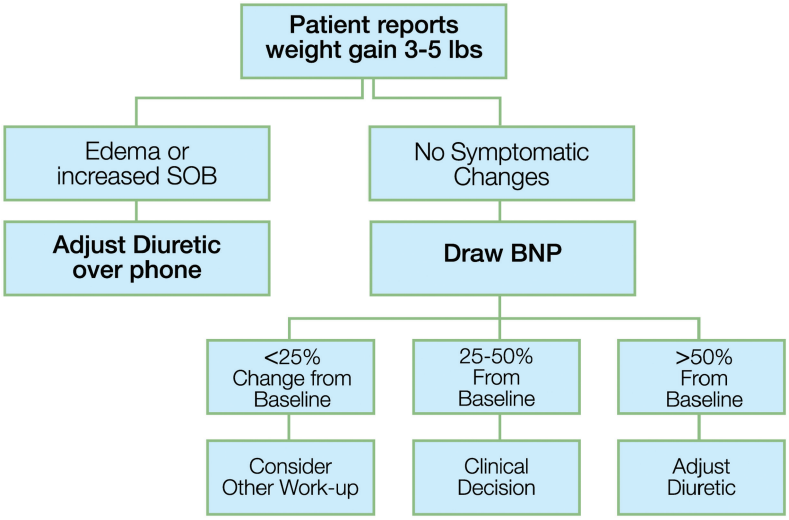


Fig. 9. Algorithms for determining decompensation.

vide a means to monitor the effects of treatment. Furthermore, it is anticipated that advances in imaging will be combined with new knowledge of biomarkers to enhance diagnosis and monitoring of therapy across the spectrum of CRS.

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