Heart Fail Rev (2014) 19:267–284
DOI 10.1007/s10741-013-9391-x

Clinical relevance of biomarkers in heart failure and cardiorenal syndrome: the role of natriuretic peptides and troponin

Alberto Palazzuoli · Serge Masson · Claudio Ronco · Alan Maisel

Published online: 7 April 2013

Abstract In recent years, numerous biomarkers have been studied in heart failure to improve diagnostic accuracy and identify patients at higher risk. The overall outcome remains fairish despite improvements in therapy, with mean survival after first hospitalization, around 5 years. We therefore need surrogate end points to better understand the pathogenetic mechanisms of the disease, including interplays with other organs. The kidney plays an important role in the initiation and progression of HF, and around one-third of patients with HF show some degree of renal dysfunction. In addition, treatment for HF often worsens renal function, consequently to hemodynamic and clinical improvement do not correspond an effective improvement in HF prognosis. Association between HF and renal impairment (RI) is now classified as cardiorenal syndrome (CRS) pointing out the bidirectional nature of this vicious circle leading to a mutual and progressive damage of both organs. The clinicians can rely on circulating biomarkers that give insights into the underlying pathogenetic mechanisms and help in risk stratification. Recently, a multimarker strategy including biomarker tool to traditional risk scores has been purposed and applied: Although each biomarker provided incremental outcome benefit, the combination of multiple biomarkers should offer the greatest improvement in risk prediction. Natriuretic peptides (NP) and cardiac troponins (TN) are the two biomarkers most studied in this setting, probably because of their organ-specific nature. However, both NP and TN cutoffs in presence of renal dysfunction need to be revised and discussed in relation to age, gender and stage of RI. In this context, the biomarkers are a unique opportunity to elucidate pathophysiological mechanisms, tailor clinical management to the single patient and improve outcomes. Specific studies about the exact role of biomarkers as in HF as in CRS should be planned and considered for future trials.

Keywords Natriuretic peptides · Troponin · Heart failure · Renal dysfunction · Biomarkers

A. Palazzuoli (✉)
Department of Internal Medicine and Metabolic Diseases, Cardiology Section, Le Scotte Hospital, University of Siena, Viale Bracci, 53100 Siena, Italy
e-mail: palazzuoli2@unisi.it

S. Masson
Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche "Mario Negri", IRCCS, Milan, Italy

C. Ronco
Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy

A. Maisel
San Diego Veterans Affair Medical Center, University California, San Diego, CA, USA

Introduction

Heart failure (HF) has an important impact in the healthcare system, and its incidence is raising in the elderly people. It is estimated that HF currently affects 0.4–2 % of the general population. The prevalence of HF in people over 65 years of age is ranging from 6 to 10 % [1, 2].

Heart failure is a complex, progressive pathophysiological condition that is primarily triggered by an initial cardiac dysfunction and fueled by a vicious circle between compensatory neurohormonal activation and progressive cardiac remodeling. Many factors including myocardial dysfunction, renin-angiotensin-aldosterone system activation (RAAS), nervous sympathetic overdrive (SNS),

endothelin, vasopressin and inflammatory systems spillover contribute to HF impairment and plasma volume retention. Its clinical presentation depends on hemodynamic status, primary cardiac disorder, systemic pressure and organ perfusion/damage [3, 4]. Among the organs affected in the HF syndrome, the kidneys represent one of the most important targets. Both organs concur to maintain the hydrosaline homeostasis and cardiocirculatory equilibrium through several autocrine and paracrine mechanisms. For this reason, it is not surprising that one-third of patients with HF show renal dysfunction and that during acute phases and re-hospitalization, around 50 % of them experience a worsening renal function (WRF) [5, 6]. Association between HF and RI is now classified in academic way as cardiorenal syndrome (CRS) pointing out the bidirectional nature of the heart/kidney interaction, as the enhancement of this vicious circle leading to progressive damage and dysfunction. Despite their high prevalence and mortality, HF and CRS remain poorly defined and vastly understudied [7]. A description of heart-kidney interaction is critical to the understanding of the overall burden of disease for each of the proposed CRS subtypes, their natural history, associated morbidity and mortality and potential health resource implications. In this sense, biomarkers should help to categorize and identify underlying causal mechanisms and their associated risk profile [8]. Early diagnosis is very important for therapy optimization and to improve the outcomes. The ability to recognize cardiac insufficiency at an early stage as well as other organs' involvement and eventual comorbidities depends on the specificity, sensibility and accuracy of the tools used. For this reason, there is an increasing interest in the development of new biomarkers. The role of circulating biomarkers in patients with cardiovascular diseases has grown exponentially over the last 10 years. Among the variety of circulating biomarkers studied (cardiac injury, adrenergic overdrive, inflammation and systemic organ damage), the only two that have shown promising clinical and prognostic impacts are the natriuretic peptides (NP) and troponins (Tn) [9]. In this review, we will describe the role of these two markers in the management of HF and CRS; we will also briefly discuss about the potential interest for other biomarkers in renal dysfunction and their prognostic relevance.

Natriuretic peptides in heart failure

B-Type natriuretic peptide (BNP) and its precursors NT-proBNP are hormones secreted predominantly by the ventricles, and their circulating concentrations are elevated in patients with chronic or acute HF. BNP is synthesized in the cardiac myocyte as a reaction to ventricular and atrial wall distension and stretching and neurohormonal activation. The cardiomyocytes synthesize a pre-propeptide (pre-proBNP 134 amino acids) which is split into a signal peptide and a propeptide (proBNP 108 amino acids). During secretion, proBNP is split at a ratio of 1:1 into the physiologically active BNP (32 amino acids), which corresponds to the C-terminal fragment, and the biologically inactive N-terminal fragment (NT-proBNP, 76 amino acids) [10]. NP convey a multitude of actions at the cardiac and renal levels including vascular smooth muscle cell relaxation, promotion of natriuresis and diuresis, direct neurohormonal antagonism on the RAAS, as well as direct myocardial effects. In concert, NP achieve a more favorable neurohormonal and hemodynamic state [11]. Elevated peptide levels are directly correlated with prognosis, HF symptoms, intraventricular pressure, pulmonary pressure and inversely proportional to cardiac output [12].

Natriuretic peptides testing are now part of the current Heart Failure Guidelines for their high sensibility and accuracy in identifying patients with any degrees of cardiac dysfunction [13]. Most of the early studies on BNP have focused on the diagnostic role of plasma BNP and NT-proBNP in patients with signs and symptoms of HF. In the Multicenter Breathing Not Properly (BNP), the gold standard for HF diagnosis was adjudicated by two independent cardiologists unaware of the laboratory results, who reviewed all the clinical data and standardized scores. BNP levels increased progressively with NYHA functional class. Concentrations above 100 pg/mL diagnosed HF with a sensitivity and specificity of 90 and 76 %, respectively, and a diagnostic accuracy of 81 % in patients admitted to the emergency department for dyspnoea [14]. Maisel et al. showed that BNP measurement together with clinical evaluation versus clinical assessment alone reduced the recovery period and the total cost of treatment. Similar findings were reported by Lainchbury et al. showing that concentrations of NT-proBNP were considerably higher among patients with acute HF compared with those who had a dyspnea due to other causes. Importantly, in this and in subsequent trials of patients with acute symptoms, the optimal NT-proBNP concentration for diagnosis of acute HF was considerably higher than those observed with outpatients. In this study, investigators compared the NT-proBNP assay (Roche Diagnostics, Indianapolis, IN, USA) with the Biosite BNP assay (SanDiego, CA, USA) and demonstrated identical areas under the receiver-operating characteristic (ROC) curve (0.89 for both), demonstrating equivalence of the 2 assays for the evaluation of the patient with acute symptoms [15]. Several multicenter studies confirmed the important role of NP in the HF diagnosis and its prognostic value [16, 17]. HF diagnosis often remains difficult, even with a comprehensive physical examination. Symptoms such as dyspnea or fatigue are non-specific and poorly sensitive

indicators for early HF that can be largely undetected. The discovery of natriuretic peptides NP as diagnostic biomarkers has been one of the most critical advances for HF diagnosis [18]. Clinicians have difficulty with appropriate triage and disposition of HF patients, evidenced by a 90 % admission rate nationwide. The REDHOT (Rapid ED Heart Failure Outpatient Trial) study demonstrated this dissociation between clinical severity and BNP levels. Among the patients admitted for acute heart failure (AHF), 11 % had BNP levels of 200 pg/mL (66 % which were perceived as NYHA III/IV), which conferred a 90-day mortality rate of 9 versus 29 % if levels were C200 pg/mL [19]. BNP measurement before discharge was effective in predicting rehospitalization whereas a BNP <250 pg/mL on discharge had favorable event-free outcomes, Thus, NP are not only a good marker for the diagnosis of HF but is also an excellent indicator of the severity of CHF as BNP values increase linearly in relation to the stage [20].

Natriuretic peptides and outcome

Plasma BNP and NT-proBNP can provide useful information in addition to clinical assessment and imaging, in the risk stratification and prognostication for patients with chronic heart failure and especially to monitor those with more severe stages [21]. Increased plasma BNP also identifies patients at increased risk for sudden death and may be a better predictor than other parameters, such as ejection fraction or NYHA class [22].

The Acute Decompensated Heart Failure National Registry (ADHERE) that recruited more than 48,000 patients with ADHF showed a positive linear relationship between in-hospital mortality and levels of BNP, in both systolic and diastolic HF [23]. BNP is an effective surrogate for congestion and, in patients with ADHF, is the result of two components: a 'dry' BNP component, which represents the patient's true hydrations status (baseline euvolemic level), and a 'wet' BNP component, which represents volume overload. Patients with HF often present with increased fluid volume and congestion [11, 24]. Both information are collected by recurrent measurements so to evaluate the exact timing volume and hemodynamic status. NT-proBNP levels are related to hospital readmission and death within 6 months. Therefore, NP potentially might help clinicians in planning discharge of HF patients [25].

The first outcome data came from the Australia–New Zealand Heart Failure Trial. In approximately 300 patients with well-characterized chronic HF of ischemic etiology (left ventricular ejection fraction, LVEF <0.45) randomized to receive carvedilol or placebo, levels of NT-proBNP above the median were associated with increased risks for new decompensated CHF events [relative risk (RR) 4.7, 95 % confidence interval (CI) 2.2–10.3] and all-cause mortality (RR 4.7, 95 % CI 2.0–10.9) during 18 months of follow-up, independent of age, NYHA functional class, LVEF, previous myocardial infarction or previous HF admission. Moreover, the importance of changes over time in natriuretic peptide concentrations as a prognostic marker in patients with chronic HF has been investigated. Even in less severe stages, NP demonstrated to correlate with prognosis: In the Val-HeFT trial, a single determination of NT-proBNP above optimal prognostic cutoff value (1,078 pg/mL) at baseline had the greatest prognostic accuracy (OR 0.702, 95 % CI 0.669–0.735, $p < 0.0001$) [26]. Changes over time in the concentration of the inactive fragment NT-proBNP are similarly associated with outcome in patients with chronic HF when expressed either as continuous absolute or relative changes or as categorical changes across a threshold value [27]. More recently, mid-regional pro-atrial natriuretic peptide MR-proANP was tested in GISSI-HF trial: The addition of MR-proANP improved net reclassification for mortality when added to multivariable models based on clinical risk factors alone [28].

Changes in NP levels can also predict left ventricular remodeling after acute myocardial infarction and appear directly associated with extension of scar measured by magnetic resonance. BNP may reflect the functional significance of myocardial damage and may be considered of prognostic value. It has been related to volume wall stress geometry and function during post-infarct period, and therefore, it is able to predict anterior versus non-anterior myocardial damage [29, 30].

The value of repeated determinations of NP levels appears to be very important for monitoring the progression of heart disease and may help in evaluating the clinical effects of medical therapy.

For instance, changes in NP levels during hospitalization were independent predictors of hospital readmission within 6 months and the death of patients hospitalized for decompensated HF. This result appears more relevant with respect to the improvement in some echocardiographic parameters (ejection fraction, diastolic volume). For the above reasons, some authors propose BNP analysis for the clinical evaluation and therapy guidance of HF. In a chronic outpatients' group STARS-BNP trial, it was clearly shown that a BNP-guided strategy reduces the incidence of death and rehospitalization for HF [31]. More definitive data were reported by Cohen-Solal in acute HF: Patients with BNP reduction over 30 % after therapy showed a significant reduction in mortality and rehospitalization compared with non-responders [32]. A high pre-discharge BNP measurement was an independent marker of death or re-admission, and early treatment lowering BNP level by 30 % was associated with improved survival. These results suggest that the variation in BNP concentrations after therapy for acute HF is independent and objective predictors of therapy's monitoring and outcome (Table 1).

Troponin in heart failure

Cardiac troponins are integral parts of the cardiac muscle infrastructure and play critical roles in excitation–contraction coupling. The release of intracellular proteins from the damaged cardiomyocytes into the bloodstream is the basis for estimating extent of cardiac damage through the assay of circulating molecules and for the diagnosis of acute myocardial infarction. The precise molecular mechanisms responsible for troponin release are not perfectly understood but experimental data suggest that necrotic, and perhaps also apoptotic myocytes, loose the sarcolemma integrity and become permeable to troponin molecules. This is supported by the relation between the extent of cardiac injury (necrotic tissue at histological examination) and circulating cardiac troponins [33, 34].

Cardiac myocyte cell death occurs at a very low but continuous rate during physiologic aging (healthy individuals loose $\sim$1 g of myocardial tissue per year, corresponding to 64 million cells) and contributes to the onset of myocardial dysfunction in the elderly [35, 36]. Besides acute coronary ischemia, circulating troponin elevation may also occur in different pathophysiological situations. Conditions like strenuous exercise, sepsis, exposure to chemotherapeutic agents, decreased renal or respiratory functions are associated with troponin elevation [37]. Concomitant diseases such as chronic pulmonary obstructive disease, diabetes or hypertension, frequently associated with HF, may contribute to elevated levels of troponins in the blood. Impaired renal function is another important determinant of troponin levels [38]. Circulating cardiac troponin levels may also be elevated in diseased skeletal muscle (myopathy), possibly after the re-expression of skeletal muscle troponin isoforms detected by the antibodies used for troponin T assay [39]. Finally, the neuroendocrine systems and inflammatory processes that are chronically activated in patients with HF might contribute per se to myocyte injury and cell death and thereby to troponin release.

The first detection of cardiac troponins in the blood of patients with HF was originally published in 1997 by two independent groups [40, 41]. La Vecchia and collaborators measured circulating cardiac troponin I (limit of detection 0.3 ng/mL) in a small group of patients with acute HF or severely decompensated chronic HF and showed an association with clinical outcome. In 35 patients with severe congestive HF, Missov documented ongoing myofibrillar degradation and increased serum levels of troponin I with a high-sensitivity assay (limit of detection 3 pg/mL). Since then, the limit of detection has been lowered substantially and new, highly sensitive troponin assays (in the range of few ng/L) with good precision are now available. Circulating cardiac troponins are now measurable with these reagents in virtually all patients with acute or chronic HF [42–45]. Troponin levels have a prognostic value in patients with chronic and stable HF, even within a range of concentrations previously not measurable with conventional assays [46] (Table 2). In two large and multicenter clinical trials (Val-HeFT and GISSI-Heart Failure), baseline concentrations of troponin were associated with adverse outcome in patients with stable HF and reduced left ventricular systolic function [44, 47] independently of demographic and clinical variables. They showed an incremental prognostic accuracy compared to the benchmark biomarker natriuretic peptides [44]. There are far less data on troponins in patients with chronic HF and preserved ejection fraction [48, 49]. Troponin testing also helps in the risk stratification of patients with acute heart failure syndromes where elevations are measured with sensitive assays in almost all patients after exclusion of criteria for acute myocardial infarction [50–53]. Troponin elevation above the 99th percentile of a normal reference population has consistently been associated with adverse outcomes in chronic or acutely destabilized heart failure.

A simple circulating biomarker that could help in monitoring the progression of acute or chronic HF would be highly desirable for the clinical management in and out of the hospital. Accordingly, numerous studies have assessed the value of repeated measurements of troponin levels over time in community-dwelling older adults [55], in ambulatory patients with chronic [47, 56, 57] or acute HF [50, 58]. Although the analysis and the interpretation of serial measurements and changes over time of a biomarker concentrations are challenging and not easily comparable, most studies suggest that even small changes in troponin have prognostic significance and may help to identify patients at risk. However, the added value of serial measurements of troponin over a single determination (in particular the last available) or over other cardiac biomarkers (in particular natriuretic peptides) seems to be quite limited in several clinical contexts. The evidence available so far does not support serial measurement of troponins for risk stratification of patients with chronic HF, until a full understanding of its implementation in clinical routine will be gained [59].

Cardiorenal syndrome definition

Hospitalization for acute decompensated HF (ADHF) is associated with high rates of morbidity and mortality. Renal impairment (RI) is one of the most common associated diseases in HF patients, and it has been increasingly recognized as an independent risk factor for morbidity and mortality. Data from several sources demonstrate that approximately 20–40 % of patients with ADHF develop

Table 1 Clinical trials regarding NP levels as prognostic indicators of adverse outcome in patients with HF

Study design	Clinical setting	Number of patients	NP (subtype, reagents and measurement)	Outcome	Main findings	References
Multicenter randomized clinical trial (ADHERE)	Patients hospitalized with acute decompensated HF	48,629	BNP and/or NT-proBNP measured within 24 h of presentation	In-hospital mortality	Elevated admission BNP level is a significant predictor of in-hospital mortality in acute HF with either reduced or preserved systolic function, independent of other clinical and laboratory variables	Fonarow et al. [22]
Multicenter randomized clinical trial (ADHERE)	Patients hospitalized with ACS and acute decompensated HF	48,629	BNP and/or NT-proBNP measured within 24 h of presentation	In-hospital mortality	BNP levels > or = 840 pg/mL and increased Tn levels are adjunctive for mortality prediction	Fonarow et al. [23]
Single center prospective study	Hospitalized acute HF patients	163	BNP measured at discharge	Patients were followed up for 60 days for the occurrence of death/hospital admission	Discharge BNP levels in acute HF patients reflected volemia and disease severity; Persistently high BNP levels during hospitalization should raise the possibility of remaining congestion, which could negatively influence prognosis; The utility of BNP as prognostic marker in HF may reside on its ability to reflect multiple underlying pathophysiological disturbances.	Pimenta et al. [24]
Single center prospective study	Patients consecutively admitted to hospital because of decompensated HF	182	NT-proBNP measurement at admission and at discharge	The primary end point was death or readmission within 6 months	Variations in NT-proBNP levels are related to hospital readmission and death within 6 months; NT-proBNP levels are potentially useful in the evaluation of treatment efficacy and might help clinicians in planning discharge of HF patients	Bettencourt et al. [25]
Multicenter prospective study	Patients with chronic ischemic (LV) dysfunction	297	Plasma NT-proBNP was measured before randomization to carvedilol or placebo, added to established treatment with a converting enzyme inhibitor and loop diuretic (with or without digoxin).	The patients' clinical outcomes including mortality and heart failure events were recorded for 18 months.	In patients with established ischemic LV dysfunction, plasma NT-proBNP is independent predictor of mortality and heart failure; Carvedilol reduced mortality and heart failure in patients with higher pre-treatment plasma NT-proBNP.	Richards et al. [26]

Table 1 continued

Study design	Clinical setting	Number of patients	NP (subtype, reagents and measurement)	Outcome	Main findings	References
Multicenter randomized, placebo-controlled, double-blind, parallel-arm clinical trial (Val-HeFT)	Ambulatory patients with chronic and symptomatic HF	1,742 (of 4,053)	NT-proBNP was measured at randomization and after 4 months	All-cause mortality, HF mortality (median follow-up 24 months)	Serial determinations of NT-proBNP concentration and classification into few categories of changes according to threshold levels may be a superior strategy for risk stratification of patients with chronic and stable HF	Masson et al. [27]
Multicenter, randomized, clinical trial (GISSI-HF)	Ambulatory patients with chronic and stable HF	1,237	Mid-regional pro-atrial natriuretic peptide (MR-proANP) was measured	All-cause mortality, HF mortality (median follow-up 47 months)	In patients with chronic and stable HF, measurement of stable precursor fragment of MR-proANP provided prognostic information independent of natriuretic peptides which are currently the best biomarkers for risk stratification	Masson et al. [28]
Multicenter randomized study (STARS-BNP)	New York Heart Association functional class II to III patients with CHF	220	BNP level was measured in patients	CHF-related death or hospital stay for CHF (follow-up median 15 months)	In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages.	Jourdain et al. [31]
Retrospective study from the SURVIVE trial	Patients hospitalized with ADHF	1,038	BNP was measured at both baseline and day 5	Short- and long-term All-cause mortality (31 and 180 day)	Patients with lowered BNP on treatment for acute HF had reduced mortality risks (31- and 180-day) compared to those with little or no BNP decrease. Early lowering of BNP predicts both short- and long-term mortality risks.	Cohen-Solal et al. [32]

renal impairment, defined on the basis of RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria [5, 60]. The broad range in the reported incidence is largely attributable to the variability in the definition of WRF, differences in the observed time-at-risk and heterogeneity of study populations. However, the most important randomized trials conducted in HF tend to exclude patients with RI despite increasing recognition of the prevalence and risks with this condition. In previous study, glomerular filtration rate was the most powerful predictor of poor prognosis and rehospitalization with a greater significance than the NYHA class and left ventricular ejection fraction [61]. There are many reasons to recognize renal function in HF: the well-known clinical impact of CKD in common cardiovascular diseases, the high prevalence of this condition in HF and the need to understand the relative benefits and risks of therapy with this condition [62, 63]. Multiple mechanisms have been proposed to explain the poor outcome in CHF patients with renal insufficiency, including accelerated hypertension, left ventricular hypertrophy, increased activation of the renin–angiotensin system, reduced renal perfusion, diuretic

Table 2 Overview of circulating cardiac troponin levels for prediction of outcome in patients with HF in selected clinical studies

Study design	Clinical setting	Number of patients	Troponin (subtype, reagents and measurement)	Outcome (follow-up duration)	Main findings	References
Chronic HF						
Multicenter randomized clinical trial (Val-HeFT)	Ambulatory patients with symptomatic chronic HF	4,053	Hs-cTnT, cTnT, single measurement (at randomization)	All-cause mortality, hospital admission for worsening of HF (median follow-up 24 months)	Troponin levels detectable with a high-sensitivity assay in 92 % of patients Very low levels of troponin predict outcome, with a high discrimination	[44]
Single center prospective study	Ambulatory patients with symptomatic chronic HF	172	cTnT, serial measurement (enrollment and every 3 months for 2 years)	All-cause mortality or cardiac transplantation (mean follow-up 19 months)	The monitoring over time of cTnT may identify a subgroup of HF patients at highest risk	[56]
Single center prospective study	Ambulatory patients with systolic chronic HF	258	Hs-cTnT and hs-cTnI, single measurement (at enrollment)	Cardiac death (mean follow-up 2.6 years)	High levels of hs-cTnI can predict mortality in patients with systolic HF Hs-cTnI may perform better than hs-cTnT	[42]
Single center prospective study	Outpatients with non-ischemic chronic HF	138	Hs-cTnI, serial measurement (enrollment and 6 months)	Cardiac death (mean follow-up 4.3 years)	Troponin elevation is a useful prognostic marker in patients with non-ischemic chronic HF	[57]
Multicenter randomized clinical trials (Val-HeFT and GISSI-HF)	Ambulatory patients with symptomatic chronic HF	5,284 (4,053 in Val-HeFT, 1,231 in GISSI-HF)	Hs-cTnT, serial measurement (baseline and 3 or 4 months)	All-cause mortality, HF mortality (median follow-up 24 months for Val-HeFT, 47 months for GISSI-HF)	Changes over time of troponin levels are strongly associated with fatal outcome Incremental prognostic accuracy is limited compared to clinical variables	[47]
Single center prospective cohort study	Outpatients with chronic systolic left ventricular HF	416	Hs-cTnT, single measurement (at enrollment)	All-cause mortality, mortality or CV hospitalization (median follow-up 4.4 years)	High levels of hs-cTnT are associated with poor outcome, independently of NT-proBNP	[46]
Acute HF						
National registry of acute heart failure (ADHERE)	Patients hospitalized for acute decompensated HF	67,924	cTnI and cTnT, single measurement on admission	All-cause in-hospital mortality	Positive levels of cardiac troponin found in 6.2 % of patients on admission Positive cardiac troponin test predicts in-hospital mortality	[53]
Single center prospective study	Patients hospitalized with decompensated HF	144	Hs-cTnI, serial measurement (admission, during hospitalization and at discharge)	All-cause mortality, hospital admission for worsening of HF	Very small troponin elevations are associated with 90-day mortality and hospital readmission	[50]

Table 2 continued

Study design	Clinical setting	Number of patients	Troponin (subtype, reagents and measurement)	Outcome (follow-up duration)	Main findings	References
International multicenter observational study (ALARM-HF)	Patients hospitalized for acute HF syndromes with preserved or reduced LV ejection fraction	3,283 (837 with preserved LVEF)	cTnT, single measurement at clinical presentation	In-hospital mortality	Positive cTnT levels are associated with in-hospital outcome in patients with acute heart failure and preserved left ventricular ejection fraction	[49]
Multicenter randomized clinical trial (PROTECT Pilot Study)	Patients hospitalized for acute HF with renal insufficiency	288	cTnT, serial measurement (enrollment and days 2, 3, 4 and 7)	Dyspnea, worsening of HF, worsening of renal function	Positive troponin at baseline and conversion to positive levels were associated with worse outcomes at 60 days	[58]
Multicenter randomized clinical trial (ASCEND-HF)	Patients with acutely decompensated HF	808	Hs-cTnI, single measurement at enrollment	In-hospital and post-discharge outcomes	Troponin at enrollment associated with in-hospital length of stay and worsening of HF No association with post-discharge outcome at 30 or 180 days	[51]
Single-center prospective observational study (BASEL V)	Unselected patients presenting to ED	667	Hs-cTnI, single measurement at the time of presentation to ED	All-cause mortality (follow-up 12 months)	Hs-cTnI levels higher in patients with acute HF compared to those with non-cardiac causes of acute dyspnea Hs-cTnI correctly reclassifies 68 % of the patients in terms of mortality	[54]

resistance and volume overload secondary to impaired sodium excretion.

In recent European and American guidelines for HF, the development of renal dysfunction was considered an index of poor prognosis and, however, does not exist by now specific clinical approach for this condition [2, 13].

Recently, a newly defined classification has pointed out the bidirectional nature of the heart/kidney interaction, as the enhancement of this vicious circle leads to progressive damage and dysfunction. Interaction between heart and kidney involves several pathways including renal hypoperfusion, neurohormonal derangements, intraglomerular hemodynamic changes, altered tubule-glomerular feedback, decreased renal blood flow and GFR, increased abdominal pressure, systemic venous congestion and inflammation [64]. The term "cardiorenal syndromes (CRS)" has been defined in academic way to understand the primary organ damage of heart or kidney leads to secondary organ dysfunction. On the basis of current definition, we now recognize five subtypes of the syndromes defined as follows: (1) acute cardiorenal syndrome (Type 1): an acute worsening of cardiac function leading to renal dysfunction; (2) chronic cardiorenal syndrome (Type 2): chronic abnormalities in cardiac function leading to renal dysfunction; (3) acute reno-cardiac syndrome (Type 3): an acute worsening of renal function causing cardiac dysfunction; (4) chronic reno-cardiac syndrome (Type 4): chronic abnormalities in renal function leading to cardiac disease; (5) secondary cardiorenal syndromes (Type 5): systemic conditions causing simultaneous dysfunction of the heart and kidney [7, 65].

All these subtypes have similar pathophysiological mechanisms due to primary systo-diastolic dysfunction followed by activation of renin-angiotensin system, sympathetic activation, increased venous pressure leading to derangement in intraglomerular blood flow and increased sodium and water reabsorption. A mixed model including both afterload word and preload HF with right side dysfunction, augmented renal venous pressure, kidney congestion, tubule obliteration and renal hypoxic damage is currently deemed the most appropriate liaison [66, 67] Fig. 1.

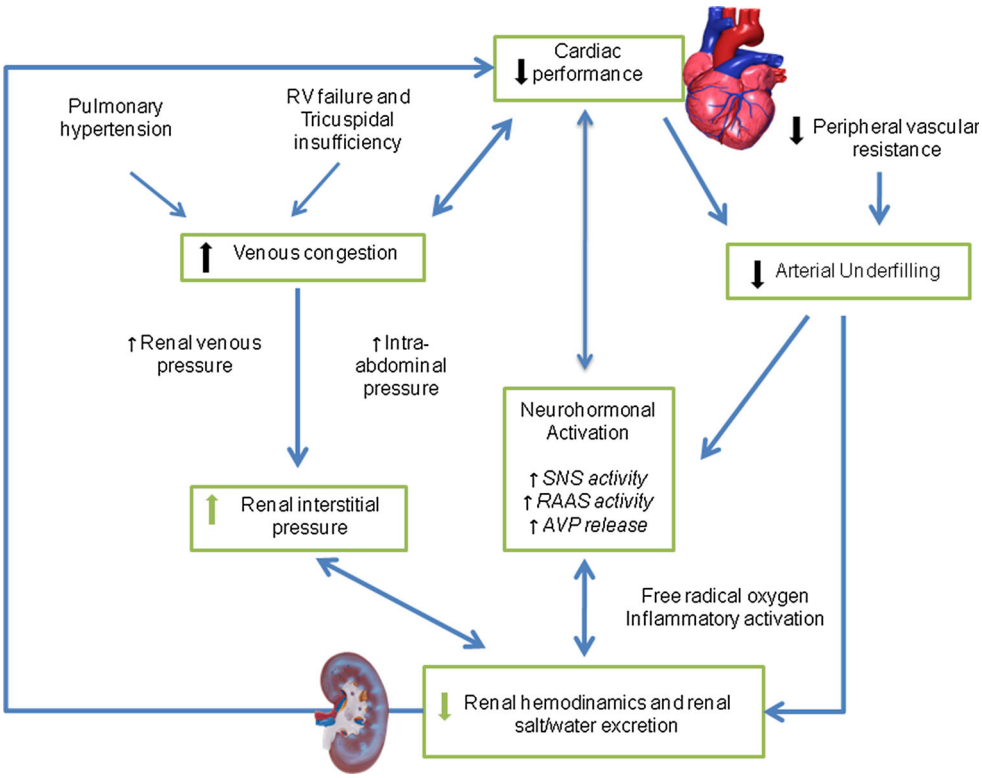

Fig. 1 Cardiorenal liaison: multiple mechanism leading to worsening outcome when heart failure is associated with any degree of renal dysfunction

All these 'actors' influence and contribute in different stages, weight and time course to CRS development and maintenance, amplifying both heart and kidney damage in a perfect pathophysiological storm.

Current and potential biomarkers of renal damage

The above cited data clearly highlight the frequent co-existence of heart and kidney dysfunction and associated poor prognosis; however, a clear laboratory cutoff definition is lacking for several reasons: First of all, definition of WRF is not uniform in terms of cutoff and methods. As reported in the meta-analysis of Damman et al. [68], a rise in serum creatinine in patients with higher basal levels has a different meaning with respect to a similar rise in patients with normal basal values. Therefore, serum creatinine (sCr) is primarily a marker of glomerular filtration but it is insensitive and unreliable to diagnose renal tubular injury in the absence of significant reduction in glomerular filtration rate (GFR). Secondly, estimated creatinine clearance is measured by several methods (mostly Cockcroft–Gault and MDRD) from plasma creatinine concentrations. Thirdly, many methodological issues are related to differences in the patient population studied, the assay and calibration of creatinine, GFR calculation and statistical metrics. MDRD is regarded as less biased and is the creatinine-based formula recommended for follow-up of patients with CKD [69]. In the setting of HF, a rise in creatinine may be interpreted as the consequence of a transient reduction in renal blood flow and thus reflects changes in renal filtration or as an acute renal tubular injury which will go through a classic period of injury, stabilization and then recovery. Therefore, increase creatinine level is poorly specific for early organ damage. Its concentration raises only after half of the kidney function is lost which may be days after the renal insult has occurred. Finally, increase in creatinine levels is not associated with outcome in all studies. The limitation of serum creatinine as prognostic indicator has been recently confirmed in a prospective study in which it was used as prospective end point [70]. Early diagnosis of renal involvement in patients with cardiac disease is of paramount importance; unfortunately, this marker cannot be used to distinguish among acute kidney injury, pre-renal azotemia and WRF [71]. Common laboratory parameters currently available are unable to diagnose the renal injury immediately after the insult to the kidney. Delay in detection also means delay in intervention in the early periods of renal injury where appropriate management strategies can be instituted before irreversible renal damage occurs.

All these troubles have prompted the research on new biomarkers able to predict acute kidney insufficiency as well as to have a clinical prognostic significance. In this sense, blood nitrogen urea (BUN), an old laboratory parameter, is re-emerging as a marker of poor prognosis

because it is considered to reflect neurohormonal activation more than renal function. BUN predicts adverse outcome independently of renal function: This finding may be explained by the concept that renal handling of urea is integral in fluid and sodium homeostasis and thus reflect neurohormonal activation: In a recent analysis of three different clinical trials, an altered urea/creatinine ratio demonstrated a worse prognosis independently of GRF values suggesting that the relationship between impaired renal function and adverse outcome depends on the mechanisms at the origin of its reduction [72]. Indeed, the renal clearance of BUN depends on the balance between urea filtration, tubular reabsorption into the collector duct and urea transport at medullary level; all these mechanisms are regulated by neurohormones such as vasopressin and by the renin-angiotensin system [73].

Several studies support albuminuria as a marker of renal dysfunction. Macroalbuminuria (defined as urine albumin: creatinine ratio [ACR] >300 mg/g) and microalbuminuria (ACR 30–300 mg/g) often precede the decline in GFR and are associated with increased CV risk in both diabetic and non-diabetic patients [74]. In CHARM study, the prevalence of microalbuminuria and macroalbuminuria and the predictive value of spot urinary albumin to creatinine ratio (UACR) for the primary composite outcome (i.e., death from cardiovascular causes or admission to hospital with worsening heart failure, and death from any cause) were assessed. Of 2,310 patients, 704 (30 %) had microalbuminuria, and 257 (11 %) had macroalbuminuria. The prevalence of increased UACR was similar in patients with reduced and preserved left ventricular ejection fractions. Patients with an increased UACR were older, had more cardiovascular comorbidity, worse renal function and a higher prevalence of diabetes mellitus than did those with normoalbuminuria. However, a high prevalence of increased UACR was still noted among patients without diabetes, hypertension or renal dysfunction [75]. Similar results were reported in another large-scale clinical trial of patients with chronic HF [76]. Elevated UACR was associated with increased risk of the composite outcome and death even after adjustment for other prognostic variables including renal function, diabetes. Therefore, microalbuminuria discerns cardiovascular risk in population with chronic renal disease independently from GFR values [77].

Novel renal biomarkers

Several studies have also recently proposed clinical use of serum neutrophil gelatinase–associated lipocalin (NGAL) levels in patients admitted in hospital with acute decompensated HF (ADHF), to estimate the risk of early worsening renal function. NGAL is produced by the nephron in response to tubular epithelial damage and is considered an early marker for acute renal tubular injury in several clinical settings [78, 79]. Aghel et al. [80] observed higher serum NGAL levels on admission in patients who developed WRF versus those who did not (194 [IQR 150–292] ng/mL vs. 128 [IQR 97–214] ng/mL, $p = 0.001$). They showed that patients with admission NGAL values $\geq$140 ng/mL had a 7.4-fold higher risk to develop WRF, with a sensitivity and specificity of 86 and 54 %, respectively. The GALLANT prospective trial shows that plasma NGAL is a good prognostic biomarker of poor outcome at early stages in patients with acute heart failure adding new information with respect to BNP measurement. The combined measurement of blood BNP and NGAL levels seem to increase the prognostic accuracy in patients with HF; NGAL might have better predictive ability compared to BNP, as it is impaired earlier and more frequently in cases of poor prognosis [81]. There is an interesting relationship between serum NGAL levels and eGFR in the setting of acute HF. Poniatowski et al. [82] have recognized serum and urine NGAL as sensitive early markers of renal dysfunction in patients with chronic HF and normal serum creatinine but reduced eGFR. Besides, NGAL appear to be a marker of renal dysfunction and useful to identify patients at early stages of CRS. Alvelos et al. [83] have investigated the performance of NGAL in the early detection of type 1 cardiorenal syndrome in patients with acute HF. They found a connection between NGAL and type 1 cardiorenal syndrome, with a cutoff value of 170 ng/L, able to predict straightforward renal insufficiency in patients with preserved renal function at admission.

Cystatin C is low molecular weight protein freely filtered by the glomerulus, reabsorbed and catabolized completely by proximal convoluted tubule, not actively secreted in urine. It can be measured in both serum and urine with commercially available tests [8]. 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, where it may be a better surrogate marker of GFR compared to creatinine [84]. In adult patients undergoing cardiac surgery, urinary CysC detects AKI within 6 h after surgery while its serum levels can identify patients who develop renal impairment C better than creatinine clearance. In a larger study with 292 patients, CysC had an AUC of 0.92 for the detection of CRS type 1. An increase in serum CysC greater than 0.3 mg/dL 48 h after admission had a specificity of 90 % and a sensitivity of 77 % for AKI. Furthermore, high serum CysC levels were also associated with a poor prognosis despite normal or mildly reduced renal function [85]. A cutoff value of 1.30 mg/dL showed a sensitivity of 75.6 % and a specificity of 68.3 % in predicting mortality and adverse clinical events, especially coronary artery disease. In acute HF, CysC level was significantly associated with

risk of death or rehospitalization during 1-year follow-up. It remained significant after adjusting for age, race, sex, comorbidities and creatinine. CysC also offered complementary prognostic information compared to the other cardiac biomarkers like troponin T, high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide, helping clinicians with more accurate risk stratification of patients with acute HF.

Kidney injury molecule-1 (KIM-1) is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells. Urinary KIM-1 seems to be highly specific for ischemic AKI and not for pre-renal azotemia. It is involved in the differentiation of T-helper cells and expressed on the proximal tubule apical membrane cilia with injury but not in the normal kidney. 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 [86]. Liangos et al. [87] performed a similar study in 103 subjects after CPB surgery; urinary KIM-1 achieved the best predictive performance with an AUC of 0.78. These studies highlight the importance of using a multimarker strategy in the emergency setting, for prediction of kidney injury development in patients with acute HF [88].

Interleukin 18 (IL-18) is an 18-kD a proinflammatory cytokine originating from proximal tubular epithelial cells. It is up-regulated during endogenous inflammatory processes. It displays sensitivity and specificity for ischemic AKI with an AUC >90 % with increased levels 48 h prior to the increase in serum creatinine [89]. It is poorly specific for acute damage but its measurement together with other more specific biomarkers could help clinicians to early identify patients who will experience a CRS (Table 3).

Natriuretic peptides in cardiorenal syndrome

Natriuretic peptides are established biomarkers in HF diagnosis and prognosis; however, increased levels can be caused by renal dysfunction as well. Indeed, because cardiac and renal dysfunctions are intricately linked, NP have the potential to serve as a valuable diagnostic and prognostic tool in several CRS types [90]. Patients with CKD have higher levels of NP than normal subjects and although some of this is attributed to reduced renal clearance. Patients with HF compared with those with HF and associated RI show higher NP levels within each NYHA class. Mean increase is around one-third with respect to subject with preserved renal function. The exact mechanism remains to be elucidated: Increased myocardial wall stress, left ventricular hypertrophy, coronary disease and cardiac remodeling are all potential contributors to NP increase in the setting of CRS. In a sub-study of the Breathing Not Properly trial evaluating the relation with renal function with a point-of-care assay for BNP, the optimal cutoff level for the diagnosis of HF was 100 pg/mL, but increased threefold in patients with an eGFR <60 mL/min/m^2 [91]. Similar findings were reported for NT-proBNP by Januzzi et al. [16] in the PRIDE study, and 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. However, NP levels may depend on other variables as age, sex, stage of renal dysfunction and timing of RI development; in line with this, the optimal NT-proBNP cut-points for identifying CHF appeared to be age dependent: <450 pg/mL for subjects <50 years, 900 pg/mL for subjects ≥50 but <75 years and 1,200 pg/mL for patients ≥75 years: 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 1,200 pg/mL for patients with an eGFR <60 mL/min/1.73 m^2. When this cutoff criterion was adjusted based upon the receiver-operating characteristic (ROC) curves for a cutoff value of 1,200 pg/mL, sensitivity remained similar (89 %) and specificity improved to 72 % [63]. Therefore, in patients

Table 3 Protein biomarkers for early detection of acute kidney injury and heart failure

Biomarker	Associated Injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal post-renal AKI
Cytokines (IL-6, 8, 18)	Delayed graft function, inflammatory activity
Troponin T	Myocardial injury, hemodynamic overload
Actin, actin depolymerizing factor	Ischemia and delayed graft function
BNP	Hemodynamic overload, neurohormonal activity
NT-proBNP	Hemodynamic overload, neurohormonal activity
Cystatin C	Proximal tubule injury

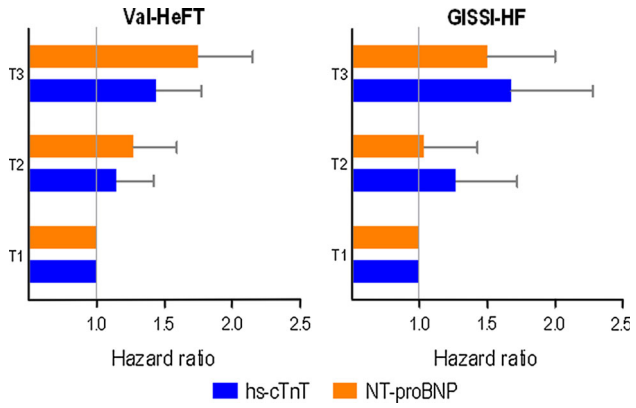

Fig. 2 BNP levels increase together within patients with heart failure relation among BNP and renal function in the diagnosis of HF. BNP levels increase with estimated glomerular filtration rate (eGFR) reduction. Modified by the Breathing Not Properly Study. The association between tertiles (T) of relative changes over time in Valsartan Heart Failure Trail (Val-HeFT, 3,474 patients, 4-month changes) and GISSI-Heart Failure trail (GISSI-HF, 1,066 patients, 3-month changes) and subsequent all-cause mortality was compared for high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal probrain natriuretic peptide (NT-proBNP). Data are shown as hazard ratio and 95 % CI with respect to first tertile considered as referent. Adjusted *p* for trend across tertiles. Val-HEFThs-cTnT (0.0009), Val-HeFTNT-proBNP (<0.0001), GISSI-HFNT-proBNP (0.31)

with severe renal insufficiency, the same cutoff appeared to be sensitive and specific enough to diagnose HF. Finally, the combination of NT-proBNP levels and creatinine clearance is highly prognostic in acute HF. NP are increased not only in CRS type 1 and 2 but even in CRS 4 in which BNP was useful marker for detecting acute HF in patients with Chronic RI and it appear able to predict cardiac events with an optimal cutoff point of 1,025 pg/mL [92] (Fig. 2).

However, the exact relationship between BNP, renal function and the severity of HF remain to be clarified. 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, but it is unknown which could be the correct cutoff values for discriminating subjects with only RI and those with CRS. This field requests specific study measuring in a different setting and CRS subtypes the diagnostic and prognostic role of NP.

Troponin in cardiorenal syndrome

It has been argued that circulating troponin levels are commonly elevated in patients with impaired renal function in the absence of an acute coronary syndrome [93–95]. Although high levels have been observed in the setting of even minor degrees of renal dysfunction, they remain associated with cardiovascular events across a whole spectrum of renal impairment. In a large study involving more than 7,000 patients with suspected acute coronary syndrome from the GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries) trial, an abnormally elevated troponin T level was predictive of an increased risk of myocardial infarction or death regardless of creatinine clearance, even if there was a very small number of patients with severe or end-stage renal disease [96]. More recently, an analysis of PREVEND (Prevention of Renal and Vascular ENd-stage Disease), a large prospective cohort study investigating the natural course of albuminuria and its relation to renal and cardiovascular disease showed that high-sensitive troponin T (and N-terminal proBNP) were independently associated with estimated glomerular filtration rate and urinary albumin excretion [97]. Despite this association, higher circulating concentrations of these two cardiac markers predicted worse cardiovascular outcome, even after adjustment for estimates of renal function. This clearly suggests that elevated troponin (or natriuretic peptide) levels in subjects with chronic kidney disease (stages 1–3) should not be solely regarded as a consequence of decreased renal clearance but as a risk for future cardiovascular events (Fig. 3).

Interpretation of cardiac biomarkers, and in particular troponin, in the setting of chronic kidney disease has been controversial. In asymptomatic dialysis patients, the two cardiac biomarkers (natriuretic peptide and troponin) are elevated and often better predictors of mortality than commonly used renal biomarkers and clinical risk factors [98, 99]. Cardiac troponin levels are frequently several-fold higher than the 99th percentile of a healthy general population in outpatients with chronic kidney disease without

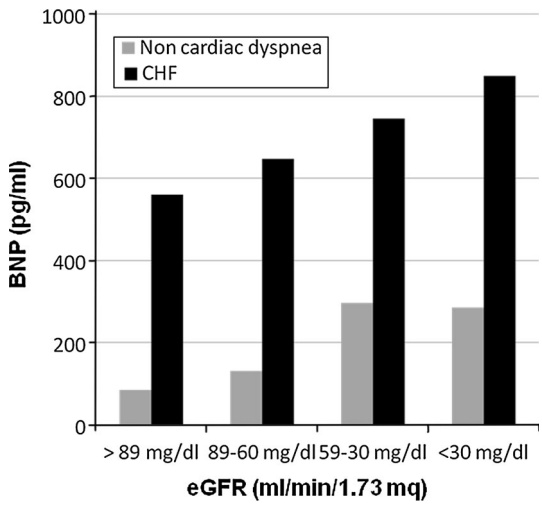

Fig. 3 Association between relative changes over time of two cardiac biomarkers (hs-cTnT and NT-proBNP) and mortality in the Val-HeFT and GISSI-HF trials

acute coronary syndromes [100] or symptoms of heart failure [101]. They may be associated with cardiovascular events and higher mortality. Potential mechanisms to explain the association between renal dysfunction and myocardial injury with elevated troponin levels include both cardiac injury and decreased renal clearance. A causal link between renal impairment and cardiac dysfunction may involve the fibroblast growth factor-23 (FGF-23), a hormone that controls phosphorus homeostasis. FGF-23 is up-regulated and directly provokes left ventricular hypertrophy in experimental models of CKD [102]. It is independently associated with left ventricular mass in the general population [103], in patients with CKD [104, 105] and in those with hemodialysis [106]. FGF-23 predicts adverse outcome in these patients [107–110]. This may therefore be an important link to explain the interplay between impaired renal function and elevated levels of cardiac troponin on mortality. On the other hand, while transcardiac gradients (cardiac production) of troponin T are similar in patients with chronic HF with or without CKD, concentrations in the aortic root are higher in patients with kidney disease [38]. This supports the hypothesis that decreased clearance contributes to troponin elevation in chronic HF.

Conclusions and future perspectives

Despite clinical progress in the treatment of HF, it remains a complex disease with poor prognosis affecting mostly older people and patients with several comorbidities. Among the frequent comorbidities, renal dysfunction is one of the most common complications and it may deserves a specific approach to evaluate its degree, timing and progression. Common strategy in HF management is focused mainly on symptoms and congestion improvement, underestimating the contribution of renal dysfunction. Indeed, interventional trials on acute HF did not demonstrate any prognostic benefit, nevertheless, an apparent hemodynamic improvement. Such results should be partially explained by the worsening renal function during early treatment phases. Therefore, persistent high-risk mortality after acute phases underscore the importance of risk stratification in this field. In this context, the study of laboratory tools able to recognize both renal and cardiac damage appears mandatory. In addition, serial biomarker measurement is becoming surrogate end points to identify responders, patients and safety of new drugs [111]. For these reasons, recently, a multimarker strategy including biomarker tool in addition to traditional risk scores has been proposed and applied: Although each single biomarker provided incremental value, their combination showed the greatest improvement in risk prediction above the established risk factors [112]. NP and troponin could reflect hemodynamic stress and cardiac damage, respectively, and serial assays should be encouraged particularly during hospitalization phase. Because they are metabolized by kidney, they should also be considered as a mirror of renal function and tested together with other specific biomarkers of tubular and glomerular damage. Measurement of traditional and new laboratory parameters might allow an early detection of kidney injury and underling mechanism recognition. Indeed, NP are the most widely studied biomarkers, their measurement can be encouraged, especially for clinical evaluation of dyspnea, for risk stratification of patients with established diagnosis of HF, but they should be used as an addition to traditional clinical approach. Elevated NP levels are currently used to diagnose HF, and as a guide to therapy in patients with HF: NP reflect neurohormonal activation as well as myocyte stress and hemodynamic impairment. Moreover, in patients with impaired renal function or CKD, increased levels should be considered as markers of reduced filtration and metabolism. However, actually specific studies evaluating this setting are lacking and should become a new target to better evaluate the clinical impact and importance of NP in patients with CRS. NP appear also potential candidates for early evaluation of end-stage renal dysfunction in patients with established CKD: Because they are frequently increased, they could be considered as early biomarkers able to identify patients with sudden and severe renal function impairment.

Another potential NP role, not completely addressed, is about the guide and monitoring HF therapy: Despite positive BATTLESCARRED findings indicating a positive results in patients with hormone guided therapy, TIME-CHF Trials did not observe any benefits respect to patients with symptom-guided treatment [113, 114]. For these reasons, the current body of evidence must be adequately powered to assess this aspect, even though a recent meta-analysis has demonstrated that the use of NP to guide pharmacologic therapy significantly reduces mortality and HF-related hospitalization in patients with chronic HF [115].

Troponin increase is a direct consequence of myocyte loss through both necrotic and apoptotic death leading to progressive cardiac enlargement and dysfunction. Therefore, it is increased in presence of AKI because of sudden increased wall stress, altered calcium handling, inflammatory activation and reduced degradation. Although both NP and troponin have a well-documented role in risk stratification and cardiac damage evaluation in HF, their importance in CRS setting should be deeply studied and defined, reclassifying cutoff criteria in relation to age gender, stage of renal disease, timing instauration and primitive cardiac defects.

Currently, the most practical use of troponin measurements is possibly as direct markers of cardiac myocyte injury, in both experimental and clinical settings. A number of clinical studies are indeed currently testing circulating cardiac troponin levels in patients undergoing chemotherapy. Cardiac toxicity of traditional and novel chemotherapeutic agents may progressively lead to left ventricular dysfunction and ultimately to HF. Troponin release in the bloodstream is becoming a surrogate end point for the studies that test the protection afforded by various classes of drugs (ACE inhibitors, beta-blockers, aldosterone antagonists) in these patients. Circulating troponins are also proposed as efficacy and safety end points for monitoring cardiac injury in invasive procedures and general surgery [116, 117].

The role of circulating cardiac troponins for the diagnosis of acute myocardial infarction is undisputed even if the introduction of new reagents with high sensitivity has challenged the clinicians and must be interpreted in the context of the clinical presentation for suspected MI. The clinical usefulness of troponins in HF is less clear. There are now good evidences, coming from well-designed, independent and adequately powered clinical studies that circulating troponins are associated with outcome in patients with HF [118] and may also be included in risk prediction models [119]. Whether troponins are superior to natriuretic peptides, the benchmark biomarkers for prognosis have not always been tested with sufficient attention, but the data available so far suggest that these markers are (at least) equivalent.

Important criteria for the clinical adoption of a biomarker for use in HF patients have recently been proposed [120]. They include analytical requisites and the reflection of pathophysiological processes involved in HF presence and progression. Candidate biomarkers must also provide clinically useful information for caregivers that should not merely recapitulate clinical information already available and must be incremental to other biomarkers. So far, only natriuretic peptides meet these standards criteria, even if their use in HF management is still debated [120, 121]. Though high-sensitivity cardiac troponin measurement could in theory be leveraged for monitoring chronic HF stability, we are far from having established its practical clinical usefulness. In particular, it remains to be validated if circulating troponins may be used as surrogate end points in clinical trials with HF patients. Even more elusive is their possible role in HF guided therapy.

Overall, a multimarker strategy including both NP and troponin measurement should be encouraged because they provide complementary prognostic information with respect to traditional approach. This cohort includes ambulatory patients with HF, patients with preserved and reduced systolic function, and wide range of HF degrees [122]. In this context, also, patients with CRS should be included to better evaluate renal dysfunction timing and etiology together with other traditional and new biomarker tool. Prospective studies and designs should be encouraged to ascertain a broad applicability to predict adverse outcome in a wide variety of patients with HF.

References

1. Gheorghiade M, Pang PS (2009) Acute heart failure syndromes. J Am Coll Cardiol 53:557–573
2. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW (2009) 2009 Focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American college of cardiology foundation/America heart association task force on practice guidelines: developed in collaboration with the international society of heart and lung transplantation. Circulation 119: 1977–2016
3. Floras JS (2009) Sympathetic nervous system activation in human heart failure clinical implications of an updated model. J Am Coll Cardiol 54:375–385
4. Gheorghiade M, De Luca L, Bonow RO (2005) Neurohormonal inhibition in heart failure: insights from recent clinical trials. Am J Cardiol 96:3L–9L
5. Heywood JT, Fonarow GC (2007) High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE Database. J Card Fail 13:422–430
6. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM (2006) Renal impairment and outcomes in heart failure systematic review and meta-analysis. J Am Coll Cardiol 47:1987–1996
7. Ronco C, McCullough P, Anker SD et al (2010) Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 31:703–711
8. Maisel A, Katz N, Hillege HL, Shaw A, Zanco P, Bellomo R et al (2011) Biomarkers in Kidney and heart diseases. Nephrol Dyal Transpl 26:62–74
9. Braunwald E (2008) Biomarkers in heart failure. N Engl J Med 358:2148–2159
10. Cheung BMY, Kumana CR (1998) Natriuretic peptides-relevance in cardiac disease. JAMA 280:1983
11. Maisel AS, Choudhary R (2012) Biomarkers in acute heart failure-state of the art. Nat Rev Cardiol 9:478–490
12. Silver MA, Maisel A, Yancy CW, McCullough PA, Burnett JC Jr, Francis GS et al (2004) BNP Consensus Panel 2004: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail 10(5 Suppl 3):1–30
13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M et al (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 33:1787–1847
14. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P et al (2002) Breathing Not Properly multinational

study investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347:161–167
15. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM (2003) Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 42:728–735
16. Januzzi JL Jr, Camargo CA, Anwaruddin S et al (2005) The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 95:948–954
17. Daniels LB, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50:2357–2368
18. Palazzuoli A, Antonelli G, Quatrini I, Nuti R (2011) Natriuretic peptides in heart failure: where we are where we are going. Intern Emerg Med 6:63–68
19. Maisel A, Hollander JE, Guss D et al (2004) Primary results of the rapid emergency department heart failure outpatient trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol 44:1328–1333
20. Silver MA, Maisel A, Yancy CW et al (2004) BNP Consensus Panel 2004: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail 10(Suppl 3):1–30
21. Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, Hasin Y, Biasucci LM (2012) Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the study group on biomarkers in cardiology of the ESC working group on acute cardiac care. Eur Heart J 33:2001–2006
22. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M (2007) Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 49:1943–1950
23. Fonarow GC, Peacock WF, Horwich TB et al (2008) Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. Am J Cardiol 101:231–237
24. Pimenta J, Paulo C, Mascarenhas J, Gomes A, Azevedo A, Rocha-Gonçalves F, Bettencourt P (2010) BNP at discharge in acute heart failure patients: is it all about volemia? A study using impedance cardiography to assess fluid and hemodynamic status. Int J Cardiol 145:209–214
25. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A (2004) N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 110:2168–2174
26. Richards AM, Doughty R, Nicholls MG, MacMahon S, Sharpe N, Murphy J, Espiner EA, Frampton C, Yandle TG (2006) Australia–New Zealand heart failure group plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. J Am Coll Cardiol 37:1781–1787
27. Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, Tognoni G, Cohn JN (2008) Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol 52:997–1003
28. Masson S, Latini R, Carbonieri E, Moretti L, Rossi MG, Ciricugno S (2010) The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. Eur J Heart Fail 12:338–347
29. Krittayaphong R, Boonyasirinant T, Saiviroonporn P, Thanapiboonpol P, Nakyen S, Udompunturak S (2008) Correlation between NT-pro BNP levels and left ventricular wall stress, sphericity index and extent of myocardial damage: a magnetic resonance imaging study. J Card Fail 14:687–694
30. Mayr A, Mair J, Schocke M, Klug G, Pedarnig K, Haubner BJ et al (2011) Predictive value of NT-pro BNP after acute myocardial infarction: relation with acute and chronic infarct size and myocardial function. Int J Cardiol 147:118–123
31. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E et al (2007) Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure. J Am Coll Cardiol 49:1733–1739
32. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A (2009) Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. J Am Coll Card 53:2343–2348
33. Fishbein MC, Wang T, Matijasevic M, Hong L, Apple FS (2003) Myocardial tissue troponins T and I. An immunohistochemical study in experimental models of myocardial ischemia. Cardiovasc Pathol 12:65–71
34. Zhang J, Knapton A, Lipshultz SE, Weaver JL, Herman EH (2008) Isoproterenol-induced cardiotoxicity in sprague-dawley rats: correlation of reversible and irreversible myocardial injury with release of cardiac troponin T and roles of iNOS in myocardial injury. Toxicol Pathol 36:277–278
35. Olivetti G, Melissari M, Capasso JM, Anversa P (1991) Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res 68:1560–1568
36. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR et al (1995) Gender differences and aging: effects on the human heart. J Am Coll Cardiol 26:1068–1079
37. Agewall S, Giannitsis E, Jernberg T, Katus H (2011) Troponin elevation in coronary vs. non-coronary disease. Eur Heart J 32:404–411
38. Tsutamoto T, Kawahara C, Yamaji M, Nishiyama K, Fujii M, Yamamoto T et al (2009) Relationship between renal function and serum cardiac troponin T in patients with chronic heart failure. Eur J Heart Fail 11:653–658
39. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS (2011) Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. J Am Coll Cardiol 58:1819–1824
40. La Vecchia L, Mezzena G, Ometto R, Finocchi G, Bedogni F, Soffiati G, Vincenzi M (1997) Detectable serum troponin I in patients with heart failure of nonmyocardial ischemic origin. Am J Cardiol 80:88–90
41. Missov E, Calzolari C, Pau B (1997) Circulating cardiac troponin I in severe congestive heart failure. Circulation 96:2953–2958
42. Tsutamoto T, Kawahara C, Nishiyama K, Yamaji M, Fujii M, Yamamoto T et al (2010) Prognostic role of highly sensitive cardiac troponin I in patients with systolic heart failure. Am Heart J 159:63–67
43. Ilva T, Lassus J, Siirilä-Waris K, Melin J, Peuhkurinen K, Pulkki K et al (2008) Clinical significance of cardiac troponins I and T in acute heart failure. Eur J Heart Fail 10:772–779
44. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T et al (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 116:1242–1249
45. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M (2012) Troponin elevation in patients with heart failure: on behalf of the third universal definition of myocardial infarction global task force: heart failure section. Eur Heart J 33:2265–2271

46. Egstrup M, Schou M, Tuxen CD, Kistorp CN, Hildebrandt PR, Gustafsson F, Faber J, Goetze JP, Gustafsson I (2012) Prediction of outcome by highly sensitive troponin T in outpatients with chronic systolic left ventricular heart failure. Am J Cardiol 110:552–557
47. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F et al (2012) Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. Circulation 125:280–288
48. Dinh W, Nickl W, Füth R, Lankisch M, Hess G, Zdunek D et al (2011) High sensitive troponin T and heart fatty acid binding protein: novel biomarker in heart failure with normal ejection fraction? A cross-sectional study. BMC Cardiovasc Disord 11:41
49. Parissis JT, Ikonomidis I, Rafouli-Stergiou P, Mebazaa A, Delgado J, Farmakis D, Vilas-Boas F, Paraskevaidis I, Anastasiou-Nana M, Follath F (2011) Clinical characteristics and predictors of in-hospital mortality in acute heart failure with preserved left ventricular ejection fraction. Am J Cardiol 107:79–84
50. Xue Y, Clopton P, Peacock WF, Maisel AS (2011) Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. Eur J Heart Fail 13:37–42
51. Felker GM, Hasselblad V, Tang WH, Hernandez AF, Armstrong PW, Fonarow GC, Voors AA, Metra M, McMurray JJ, Butler J, Heizer GM, Dickstein K, Massie BM, Atar D, Troughton RW, Anker SD, Califf RM, Starling RC, O'Connor CM (2012) Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. Eur J Heart Fail 14:1257–1264
52. Pascual-Figal DA, Casas T, Ordonez-Llanos J, Manzano-Fernández S, Bonaque JC, Boronat M, Muñoz-Esparza C, Valdés M, Januzzi JL (2012) Highly sensitive troponin T for risk stratification of acutely destabilized heart failure. Am Heart J 163:1002–1010
53. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH (2008) ADHERE investigators. Cardiac troponin and outcome in acute heart failure. N Engl J Med 358:2117–2126
54. Arenja N, Reichlin T, Drexler B, Oshima S, Denhaerynck K, Haaf P, Potocki M, Breidthardt T, Noveanu M, Stelzig C, Heinisch C, Twerenbold R, Reiter M, Socrates T, Mueller C (2012) Sensitive cardiac troponin in the diagnosis and risk stratification of acute heart failure. J Intern Med 271:598–607
55. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M et al (2010) Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 304:2494–2502
56. Miller WL, Hartman KA, Burritt MF, Grill DE, Jaffe AS (2009) Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. J Am Coll Cardiol 54:1715–1721
57. Kawahara C, Tsutamoto T, Sakai H, Nishiyama K, Yamaji M, Fujii M et al (2011) Prognostic value of serial measurements of highly sensitive cardiac troponin I in stable outpatients with nonischemic chronic heart failure. Am Heart J 162:639–645
58. O'Connor CM, Fiuzat M, Lombardi C, Fujita K, Jia G, Davison BA et al (2011) Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. Circ Heart Fail 4:724–732
59. Gaggin HK, Januzzi JL Jr (2012) What is the role of serial high-sensitivity troponin measurements in chronic heart failure? Clin Chem 58:1079–1081
60. Bagshaw S, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, Anker SD, Anand I, Bellomo R, Berl T, Bobek I, Davenport A, Haapio M, Hillege H, House A, Katz N, Maisel A, Mankad S, McCullough PA, Mebazaa A, Palazzuoli A, Ponikowski P, Shaw A, Soni S, Vescovo G, Zamperetti N, Zanco P, Ronco C; Acute Dialysis Quality Initiative (ADQI) Consensus Group (2010) Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI consensus conference. Nephrol Dial Transplant 25(5):1406–16
61. Hillege HL, Girbes AR, de Kamp J, Boomsma F, De Zeeuw D et al (2000) Renal function neurohormonal activation and survival in patients with chronic heart failure. Circulation 102:203–210
62. Palazzuoli A, Beltrami M, Nodari S, McCullough PA, Ronco C (2011) Clinical impact of renal dysfunction in heart failure. Rev Cardiovasc Med 12:186–199
63. Cruz DN, Gheorghiade M, Palazzuoli A, Ronco C, Bagshaw SM (2011) Epidemiology and outcome in cardio-renal syndrome. Heart Fail Rev 16:531–542
64. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL (2011) The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis 54:144–153
65. House AA, Anand I, Bellomo R, Cruz D, Bobek I, Anker S et al (2010) Definition and classification of cardio-renal syndromes: workgroup statements from the 7th ADQI consensus conference. Nephrol Dial Transplant 25:1416–1420
66. Ronco C, Cicoira MA, McCullough PA (2012) Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 60:1031–1042
67. Tang WH, Mullens W (2010) Cardiorenal syndrome in decompensated heart failure. Heart 96:255–260
68. Damman K, Navis G, Voors AA, Asselbergs FW et al (2007) Worsening renal function and prognosis in heart failure: a systematic review and meta-analysis. J Cardiac Fail 13:599–608
69. Lamb EJ, Tomson CR, Roderick PJ (2005) Estimating kidney function in adults using formulae. Ann Clin Biochem 42:321–345
70. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V et al (2012) Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 5:54–62
71. Cruz N, Goh CY, Palazzuoli A, Slavin L, Ronco C, Maisel A (2011) Laboratory parameters of cardiac and kidney dysfunction in cardiorenal syndromes. Heart Fail Rev 16:545–551
72. Testani JM, Coca SG, Shannon RP, Kimmel SE, Coppola TP (2011) Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. Eur J Heart Fail 13:1224–1230
73. Kazory A (2010) Emergence of blood nitrogen urea as a biomarker of neurohormonal activation in heart failure. Am J Cardiol 106:694–700
74. Schiffrin EL, Lipman ML, Mann JF (2007) Chronic kidney disease: effects on the cardiovascular system. Circulation 116(1):85–97
75. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ (2009) CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 374:543–550
76. Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, Frisinghelli A, Minneci C, Valisi M, Maggioni AP, Marchioli R, Tognoni G, Tavazzi L; GISSI-HF Investigators (2010) Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. Circ Heart Fail 3:65–72
77. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS (2011) Lower estimated glomerular filtration rate and higher albuminuria are associated with

mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int 79:1331–1340
78. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT (2008) Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 52:425–433
79. Yndestad A, Landrø L, Ueland T, Dahl CP, Flo TH, Vinge LE, Espevik T, Frøland SS, Husberg C, Christensen G, Dickstein K, Kjekshus J, Øie E, Gullestad L, Aukrust P (2009) Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. Eur Heart J 30:1229–1236
80. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH (2010) Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. J Card Fail 16:49–54
81. Maisel AS, Mueller C, Fitzgerald R, Brikhan R, Hiestand BC, Iqbal N, Clopton P, van Veldhuisen DJ (2011) Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. Eur J Heart Fail 13:846–851
82. Poniatowski B, Malyszko J, Bachorzewska-Gajewska H, Malyszko JS, Dobrzycki S (2009) Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in patients with chronic heart failure and coronary artery disease. Kidney Blood Press Res 32:77–80
83. Alvelos M, Pimentel R, Pinho E, Gomes A, Lourenço P, Teles MJ, Almeida P, Guimarães JT, Bettencourt P (2011) Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. Clin J Am Soc Nephrol 6:476–481
84. Herget-Rosenthal S, Marggraf G, Hüsing J et al (2004) Early detection of acute renal failure by serum cystatin C. Kidney Int 66:1115–1122
85. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I, Martinez-Marcos FJ, Camacho-Vazquez C, Ruiz-Frutos C et al (2011) Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 17:31–38
86. Han WK, Bailly V, Abichandani R et al (2002) Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 62:237–244
87. Liangos O, Perianayagam M (2007) Urinay NAG activity and KIM-1 level are associated with adverse outcomes in acute renal failure. JASN 18:904–912
88. Damman K, Masson S, Hillege HL, Maggioni AP, Voors AA, Opasich C, van Veldhuisen DJ, Montagna L, Cosmi F, Tognoni G, Tavazzi L, Latini R (2011) Clinical outcome of renal tubular damage in chronic heart failure. Eur Heart J 32:2705–2712
89. Parikh CR, Abraham E, Ancukiewicz M et al (2005) Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 16:3046–3052
90. Cruz D, Fard A, Clementi A, Ronco C, Maisel A (2012) Role of biomarkers in the diagnosis and management of cardio renal syndrome. Semin Nephrol 32:79–92
91. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE et al (2003) B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis 41:571–579
92. Park S, Cho GY, Kim SG, Hwang YI, Kang HR et al (2009) Brain natriuretic peptide levels have diagnostic and prognostic capability for cardio-renal syndrome type 4 in intensive care unit patients. Crit Care 13:1–11
93. Lamb EJ, Kenny C, Abbas NA, John RI, Webb MC, Price CP, Vickery S (2007) Cardiac troponin I concentration is commonly increased in nondialysis patients with CKD: experience with a sensitive assay. Am J Kidney Dis 49:507–716
94. Abbas NA, John RI, Webb MC, Kempson ME, Potter AN, Price CP, Vickery S, Lamb EJ (2005) Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. Clin Chem 51:2059–2066
95. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS (2002) Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 40:2065–2071
96. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, Mahaffey KW, Newby LK, Califf RM, Simoons ML, Topol EJ, Berger P, Lauer MS (2002) Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 346:2047–2052
97. Scheven L, de Jong PE, Hillege HL, Lambers Heerspink HJ, van Pelt LJ, Kootstra JE, Bakker SJ, Gansevoort RT; PREVEND study group (2012) High-sensitive troponin T and N-terminal pro-B type natriuretic peptide are associated with cardiovascular events despite the cross-sectional association with albuminuria and glomerular filtration rate. Eur Heart J 33:2272–2281
98. McGill D, Talaulikar G, Potter JM, Koerbin G, Hickman PE (2010) Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure. Clin Chim Acta 411:936–939
99. Gaiki MR, Devita MV, Michelis MF, Panagopoulos G, Rosenstock JL (2012) Troponin I as a prognostic marker of cardiac events in asymptomatic hemodialysis patients using a sensitive troponin I assay. Int Urol Nephrol 44:1841–1845
100. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, Wolf M, Gaggin H, Januzzi J (2012) Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. Clin Chem 58:1342–1351
101. Hasegawa M, Ishii J, Kitagawa F, Kanayama K, Takahashi H, Ozaki Y, Yuzawa Y (2012). Prognostic value of highly sensitive troponin T on cardiac events in patients with chronic kidney disease not on dialysis. Heart Vessels. 2012 Aug 23 [Epub ahead of print] PubMed PMID: 22914904
102. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M (2011) FGF23 induces left ventricular hypertrophy. J Clin Invest 121:4393–4408
103. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, Rifkin D, Siscovick DS, Sarnak MJ, Shlipak MG (2012) Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). J Am Coll Cardiol 60:200–207
104. Smith K, Defilippi C, Isakova T, Gutiérrez OM, Laliberte K, Seliger S, Kelley W, Duh SH, Hise M, Christenson R, Wolf M, Januzzi J (2012) Fibroblast growth factor 23, high-sensitivity cardiac troponin, and left ventricular hypertrophy in CKD. Am J Kidney Dis 2012 Aug 7 [Epub ahead of print] PubMed PMID: 22883134
105. Gutiérrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, Sarwar A, Hoffmann U, Coglianese E, Christenson R, Wang TJ, deFilippi C, Wolf M (2009) Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation 119:2545–2552
106. Negishi K, Kobayashi M, Ochiai I, Yamazaki Y, Hasegawa H, Yamashita T, Shimizu T, Kasama S, Kurabayashi M (2010)

Association between fibroblast growth factor 23 and left ventricular hypertrophy in maintenance hemodialysis patients. Comparison with B-type natriuretic peptide and cardiac troponin T. Circ J 74:2734–2740
107. Holden RM, Beseau D, Booth SL, Adams MA, Garland JS, Morton RA, Collier CP, Foley RN (2012) FGF-23 is associated with cardiac troponin T and mortality in hemodialysis patients. Hemodial Int 16:53–58
108. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M; Chronic Renal Insufficiency Cohort (CRIC) Study Group (2011) Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 305:2432–2439
109. Seiler S, Reichart B, Roth D, Seibert E, Fliser D, Heine GH (2010) FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. Nephrol Dial Transplant 25:3983–3989
110. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M (2008) Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 359:584–592
111. Felker MG (2011) Biomarkers as a surrogate end points in heart failure trials. Heart Fail Clin 7:501–507
112. Ky B, French B, Levy WC, Sweitzer NK, Fang JC, Wu AH, Goldberg LR, Jessup M, Cappola TP (2012) Multiple biomarkers for risk prediction in chronic heart failure. Circ Hear Fail 5:183–190
113. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG, Richards AM (2009) N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from BATTLESCARRED trial. J Am Coll Cardiol 55:53–60
114. Pfisterer M, Buser P, Rickli H, Gutmann M, Erna P, Rickenbacher P, Vuillomenet A, Jeker U, Tubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-LaRocca HP (2009) BNP guided vs symptom-guided heart failure therapy: the Trial of intensified vs standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. JAMA 301:383–392
115. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, Leosco D, Perrone-Filardi P (2013) Natriuretic Peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS ONE 8:e58287. doi:10.1371/journal.pone.0058287
116. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D, Villar JC, McQueen M, McFalls E, Filipovic M, Schünemann H, Sear J, Foex P, Lim W, Landesberg G, Godet G, Poldermans D, Bursi F, Kertai MD, Bhatnagar N, Devereaux PJ (2011) Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 114:796–806
117. Babu GG, Walker JM, Yellon DM, Hausenloy DJ (2011) Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. Eur Heart J 32:23–31
118. Nagarajan V, Hernandez AV, Tang WH (2012) Prognostic value of cardiac troponin in chronic stable heart failure: a systematic review. Heart 98:1778–1786
119. Barlera S, Tavazzi L, Franzosi MG, Marchioli R, Raimondi E, Masson S, Urso R, Lucci D, Nicolosi GL, Maggioni AP, Tognoni G, GISSI-HF Investigators (2013) Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram. Circ Heart Fail 6:31–39
120. Januzzi JL, Troughton R (2013) Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. Circulation 127:500–508
121. Desai AS (2013) Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are not useful in heart failure management: the art of medicine remains long. Circulation 127:509–516
122. Dunlay SM, Gerber Y, Weston SA, Killian JM, Redfield MM, Roger VL (2009) Prognostic value of biomarker in heart failure application of novel methods in the community. Circ Heart Fail 2:393–400