

Clinical update

Biomarkers of renal injury and function: diagnostic, prognostic and therapeutic implications in heart failure

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Heart failure guidelines suggest evaluating renal function as a routine work-up in every patient with heart failure. Specifically, it is advised to calculate glomerular filtration rate and determine blood urea nitrogen. The reason for this is that renal impairment and worsening renal function (WRF) are common in heart failure, and strongly associate with poor outcome. Renal function, however, consists of more than glomerular filtration alone, and includes tubulointerstitial damage and albuminuria. For each of these renal entities, different biomarkers exist that have been investigated in heart failure. Hypothetically, and in parallel to data in nephrology, these markers may aid in the diagnosis of renal dysfunction, or for risk stratification, or could help in therapeutic decision-making. However, as reviewed in the present manuscript, while these markers may carry prognostic information (although not always additive to established markers of renal function), their role in predicting WRF is limited at best. More importantly, none of these markers have been evaluated as a therapeutic target nor have their serial values been used to guide therapy. The evidence is most compelling for the oldest—serum creatinine (in combination with glomerular filtration rate)—but even for this biomarker, evidence to guide therapy to improve outcome is circumstantial at best. Although many new renal biomarkers have emerged at the horizon, they have only limited usefulness in clinical practice until thoroughly and prospectively studied. For now, routine measurement of (novel) renal biomarkers can help to determine cardiovascular risk, but there is no role for these biomarkers to change therapy to improve clinical outcome in heart failure.

Keywords

Renal function • Heart failure • Biomarkers • Diagnosis • Prognosis

Introduction

Fifteen years ago, two large studies were published which showed for the first time the powerful prognostic value of renal (dys) function in patients with chronic heart failure (HF) and (a)symptomatic left ventricular dysfunction.^{1,2} Of course, the crucial role of renal function in HF patients had been well recognized before, but it had received relatively little attention.^{3,4} This remarkable finding was pointed out at the time in a review on the subject, called 'The Cinderella of cardiovascular risk profile'.⁵ Since then, a large number of studies on renal function in patients with cardiovascular disease, in particular in patients with HF and after myocardial infarction have been published.^{6–8}

However, 'renal dysfunction' in this regard largely reflects a loss of glomerular filtration rate (GFR) that is estimated by formulas that have been validated to give a reasonably accurate indication of GFR.⁹

Renal dysfunction is however much more than decreased glomerular filtration alone. It consists of renal haemodynamics, filtration, sodium and water retention, proteinuria and albuminuria, tubulointerstitial injury, and regulation of calcium phosphate metabolism, all of which have been shown to be altered or impaired in HF patients.^{10,11} Renal dysfunction itself may also give rise to the development of HF. This complexity of renal function has led to the use of a large number of renal biomarkers. Although conventional biomarkers of renal injury and function, such as serum creatinine, are used in day to day practice, novel markers with promising characteristics have emerged. However, their clinical usefulness in determining diagnosis, prognosis, and therapeutic decisions is incompletely understood.

In general, biomarker research in cardiovascular disease has greatly expanded in the last decade. There are numerous markers that have been studied, and there is no exception to markers of

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renal injury and function in patients with HF. However, markers are mostly studied in regard to their prognostic implication, but often these findings do not lead to changes in clinical practice. Also, many new biomarkers have been discovered, but a clear pathophysiologic background, and thorough review of these markers is often lacking. Genome wide association studies could help in the determination of the position of a possible biomarker by combining genetic information with phenotype and information on genetic expression, but have to our knowledge not been used for renal biomarkers in HF. Importantly, to alter patient care, a (renal) biomarker in HF should either aid in the timely diagnosis of HF and/or renal injury or provide additional information on top of conventional tools and markers. Also, the position of a marker at a ‘sweetspot’ of the pathophysiology of renal dysfunction in HF would help in the understanding of the physiology and importance of the marker, and may help in its adoption by HF clinicians (Figure 1). For the present review, we will discuss the diagnostic, prognostic, and therapeutic implications of important renal markers of injury and function in HF.

Markers of glomerular filtration rate

The reason GFR is such a powerful predictor of outcome in HF is probably related to the fact that in HF, GFR is largely determined by impaired haemodynamics.^{12–15} Cody and co-workers⁴

conducted seminal studies in this field and showed that when cardiac index has decreased by only 15–20%, renal blood flow (RBF) drops by as much as 50%. At this stage, GFR also decreases, but is still relatively maintained because of an angiotensin II-mediated efferent vasoconstriction, resulting in an increase in filtration fraction. As such, activation of the renin–angiotensin–aldosterone system (RAAS) plays an important role in preserving GFR in HF. Renin–angiotensin–aldosterone system inhibitors such as angiotensin-converting enzyme inhibitors, but also beta-blockers and mineralocorticoid receptor antagonists, may thus affect GFR and RBF.^{14,16} On a population level, this results in an almost linear relationship between GFR and RBF in the presence of RAAS inhibitors.¹⁵ The gold standard of measuring GFR is by using specific (radioactive) labelled markers such as iothalamate or inulin clearance, but this method is patient-unfriendly, time-consuming, and expensive.⁹ Therefore, easily obtainable plasma markers have been used to estimate renal function; these include serum creatinine, serum Cystatin C, and blood urea nitrogen (BUN).

Serum creatinine

Diagnostic properties

Serum creatinine is the most frequently used marker of renal function (and injury), and it is often thought as synonymously with GFR/renal function. The ability of serum creatinine to provide an accurate measure of GFR is often overestimated.⁹ Serum creatinine levels are a reflection of the constant break down of skeletal muscles, and

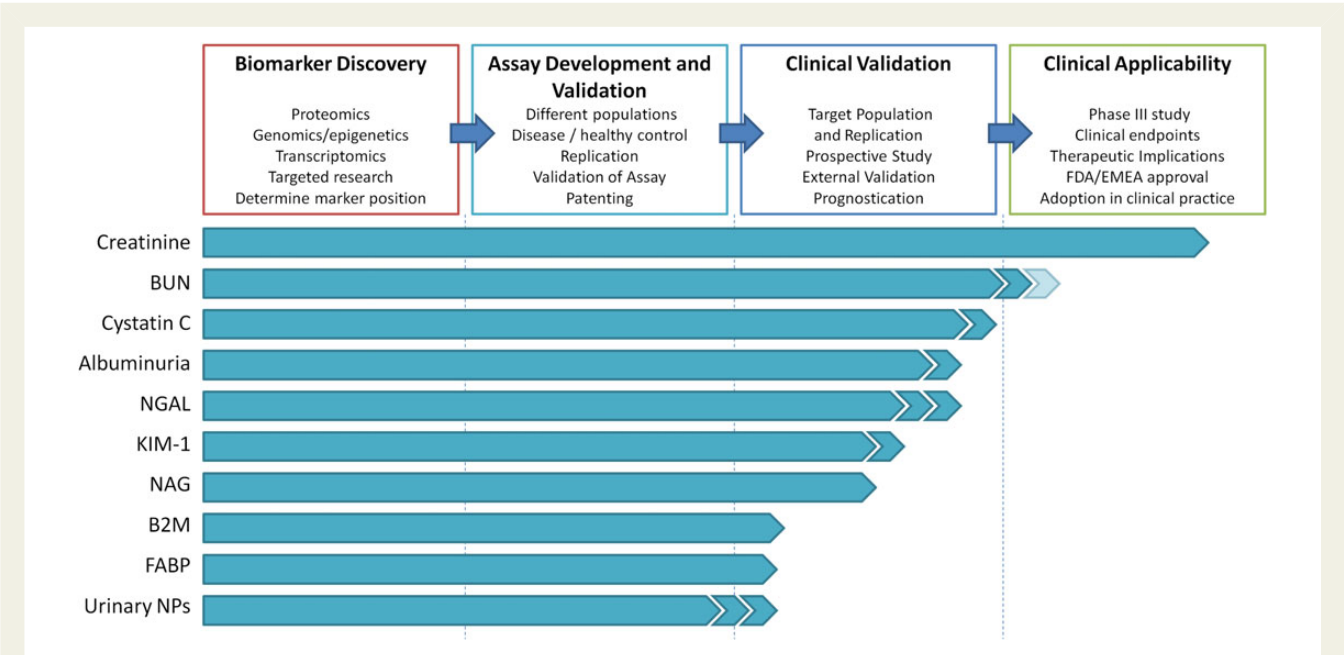


Figure 1 Renal biomarker development. Hypothetical approach to (renal) biomarker discovery and clinical applicability. Biomarkers can be ‘discovered’ via different approaches, even by chance. Once the position of the marker is assessed and defined, assays can be developed that allow accurate detection of the biomarker. After validation and replication, the marker can be evaluated in clinical cohorts, including the target population. Then, after extensive validation, internally and externally, prospective studies should be carried out to show additive importance of the use of the marker on top of conventional therapies. Eventually, the marker can be adopted into clinical practice. This whole process from discovery to adoption into clinical practice can take several years to even decades. Interestingly, none of these markers, including serum creatinine, have been investigated to such an extent that it actually ticks all these boxes. B2M, β -2-microglobulin; BUN, blood urea nitrogen; FABP, fatty acid-binding protein (types L and H); KIM-1, kidney injury molecule 1; NAG, *N*-acetyl- β -d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NP, natriuretic peptide.

since it is freely filtered by the glomerulus, it allows estimation of GFR by measuring plasma levels. There is however some active tubular secretion, making the appraisal of GFR imperfect. Additionally, the relationship between serum creatinine and estimated GFR (eGFR) is exponential, which means that small changes at both extremes of creatinine translate into different changes in GFR. Other important sources of bias exist. Body composition (including muscle mass), higher age, and female gender influence the relationship between serum creatinine and GFR.⁹ This also occurs in acute HF, where serum creatinine gives an inaccurate estimate of GFR. It is therefore important not to solely rely on serum creatinine levels to evaluate GFR, but to estimate GFR by serum creatinine (and Cystatin C) based formulas, that give a more accurate estimation. Several formulas to estimate GFR that has been constructed in nephrology have now been validated in chronic HF. Of these, the Cockcroft-Gault, which actually gives an estimate of creatinine clearance rather than GFR, demonstrates the worst accuracy.⁹ The most commonly used equation is the simplified modification of diet in renal disease (sMDRD) formula, which includes four variables (age, gender, race, and serum creatinine), and which shows acceptable precision and accuracy, but is outperformed by the full MDRD equation, that also includes BUN and serum albumin.^{9,17} Both are however less precise than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which either uses only age, race and serum creatinine or also includes Cystatin C.¹⁸ The latter showed the best precision and accuracy in chronic HF,¹⁹ but for clinical practice, the CKD-EPI equation that uses only serum creatinine is probably sufficient.

It is important to realize that serum creatinine has a special role when assessing renal injury. Kidney injury, in nephrology, is often present as a condition with progressive kidney function decline, nephron loss, azotaemia, and represents either an acute condition [acute kidney injury (AKI)] or more chronic condition with renal fibrosis and tubulointerstitial damage.²⁰ Histological evidence of actual renal injury in HF is scarce, although considered present given the presence of high levels of renal markers that associate with renal injury (as discussed below). Acute kidney injury as defined in nephrology literature is probably rare in HF, but less pronounced alterations, termed worsening renal function (WRF) develop in ~20% of all patients.^{6,10} Importantly, serum creatinine is the marker that is used to diagnose either AKI or WRF, in conjunction with other factors of deterioration.²⁰ This makes the diagnostic capabilities of serum creatinine to predict AKI or WRF difficult to interpret, as it is part of the actual diagnostic criteria. Nevertheless, patients with higher serum creatinines have a greater risk of WRF.⁶

Prognostic properties

Chronic kidney disease as estimated by decreased GFR or high-serum creatinine predicts all-cause mortality and HF rehospitalization, independent of established risk factors.^{1,2,6} Worsening renal function as determined by an increase in serum creatinine $>26.5 \mu\text{mol/L}$ and/or $>25\%$ has been associated with worse outcomes when clinical status deteriorates, the exception being when overall well-being improves or when RAAS inhibitors are introduced.^{6,21} Changes that occur during the latter situations are termed pseudo-WRF and carry less—if any—prognostic implication, with the exception of RAAS inhibitor therapy in HF with

preserved ejection fraction (HFPEF).²⁰ Persistent congestion or (in) adequate decongestion has also been suggested as important mediators of the prognostic importance of WRF. Patients with WRF without congestion at discharge or with adequate haemoconcentration do not have an increased risk of poor outcome, compared with those who have both WRF and persistent congestion or the absence of haemoconcentration.^{22,23} One limitation of serum creatinine is the fact that serum levels do not only reflect glomerular filtration, but also muscle mass. Therefore, increases in serum creatinine could theoretically also represent increases in muscle mass instead of deterioration of eGFR, which is thought to be a favourable situation in HF.

Therapeutic implications

In practice, most physicians will probably alter therapy based on changes (or baseline) serum creatinine and GFR. The dosing of drugs that are filtrated or renally cleared should be adjusted to GFR. Renin–angiotensin–aldosterone system inhibitors cause a slight decrease in GFR as part of their working mechanism¹⁶ and caution should be taken when considering adjusting dose or halting these evidence-based therapies.²⁴ Even if GFR decreases slightly during initiation of these therapies, the mortality and morbidity benefit of these therapies is largely maintained.²¹ Of course, when GFR deteriorates fast, therapies should be reassessed and possibly discontinued, as highlighted in recent guidelines.²⁴ Although no study has evaluated a creatinine-based treatment algorithm, serum creatinine has been used either as inclusion criteria or clinical endpoint. It has been proved difficult to improve serum creatinine during acute HF treatment, which may be due to the fact that changes in serum creatinine during treatment of acute HF can mean different things.²⁵ Probably if the clinical status of patients improves, increases in serum creatinines can generally be accepted, while even small increases in serum creatinine in patients with marked deterioration of clinical status should call for immediate attention, and therefore assessment of clinical status is important in each patient.²⁰

Serum Cystatin C

Diagnostic properties

Cystatin C is a small protein that is produced in all cells that contain a nucleus. Cystatin C is so small that it is thought to be freely filtered through the glomerulus, without active secretion.²⁶ There is, however, tubular reabsorption, which is thought to be impaired with tubular damage, causing larger than normal amounts of Cystatin C to appear in the urine. Therefore, in contrast to *serum* Cystatin C being thought as a sensitive marker of glomerular filtration, *urinary* Cystatin C could be regarded as a marker of tubular damage, but data in HF are limited.

Several studies have evaluated Cystatin C as a marker of glomerular filtration in HF. In one study in chronic HF, it showed a strong association with GFR determined by iothalamate clearance.²⁷ Moreover, the CKD-EPI formula that combines serum creatinine and Cystatin C was shown to have the highest accuracy and precision in determining GFR, thereby outperforming (s)MDRD and Cockcroft-Gault.¹⁹

Prognostic properties

The association between Cystatin C levels and outcome was examined in the Acute Study of Clinical Effectiveness of Nesiritide in

Decompensated HF (ASCEND-HF) study, in which Cystatin C was a prominent predictor of outcome.²⁸ Increases in Cystatin C, possibly reflecting WRF, were however not associated with poor outcomes. Other studies have confirmed these findings in other acute HF populations, including those with PEF.^{29,30} In chronic HF, Cystatin C remains a prominent predictor of outcome in multiple studies^{27,31} (see Supplementary material online, Table S1).

Therapeutic implications

No studies have used Cystatin C to guide therapy in HF, but Cystatin C has been used as (secondary) outcome measures in randomized trials, including the Cardiorenal Rescue Study in Acute Decompensated HF (CARRESS-HF) and Diuretic Optimization Strategies Evaluation (DOSE).^{32,33} Interestingly, while in these studies serum creatinine showed increases in the active treatment groups that were deemed unfavourable, Cystatin C levels did not change substantially. Given the observation that changes/increases in serum creatinine were not associated with clinical outcome in ASCEND-HF, this questions the use of serum creatinine as an outcome measure, and suggests that Cystatin C would be a better marker of GFR.

Blood urea nitrogen

Diagnostic properties

Blood urea nitrogen is closely related to renal function and neurohormonal activation in HF. Blood urea nitrogen is filtered through the glomerulus, and urea is reabsorbed in the tubules. Therefore, plasma BUN is not only dependent on GFR, but also on tubular function, and closely related to neurohormonal activity such as RAAS activity.³⁴ Urea is predominantly reabsorbed in the proximal tubules, but also more distally in the collecting ducts under stimulation of V2 receptors of vasopressin.³⁵ Multiple studies demonstrated that discordantly high BUN/creatinine ratios (either very high BUN levels irrespective of creatinine, or relatively high BUN levels compared with creatinine levels) identify different patient profiles, including those with worse outcomes.^{25,36,37}

Prognostic properties

Blood urea nitrogen is a powerful predictor of outcome in HF, but this is not always recognized. In the Placebo Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for patients Hospitalized with Acute Decompensated HF (PROTECT) study, BUN was the strongest predictor of 180-day mortality in patients with acute HF.³⁸ In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic HF (OPTIME-CHF), BUN also identified patients at risk of poor survival³⁹ (see Supplementary material online, Table S2). The reason BUN is such a strong marker of outcome is unclear, but may be related to the fact that it is not only associated with GFR, but also with RAAS activity and nutritional status.³⁴

Therapeutic implications

At this moment, it is difficult to make bold statements on the clinical usefulness of BUN, but a few studies have investigated—retrospectively—the association between BUN and diuretic use, and found striking results. Nunez et al.⁴⁰ combined Cancer Anti-125 (CA-125) as a marker of congestion, with BUN, and

showed that in patients with normal CA-125 and high BUN, high-dose diuretics were associated with poor outcome, while the opposite was observed in patients with higher CA-125. Testani et al.⁴¹ evaluated BUN in chronic HF patients and showed that high-dose loop diuretics were only associated with worse outcomes if baseline BUN was high, which may suggest that BUN could be useful in determining risk associated with high-dose loop diuretics in HF.

Makers of glomerular integrity

Albuminuria and proteinuria

Diagnostic properties

Proteinuria and albuminuria are typically linked to hypertensive nephropathies in non-HF populations. Higher intraglomerular pressures cause leakage and damage to the glomerular membrane, leading to passage of more than normal amounts and types of proteins in the urine. However, in HF, intraglomerular pressures are probably low rather than high. Other mechanisms are therefore probably involved in HF, which include endothelial damage/dysfunction, inflammation, podocyte damage, and even venous congestion.^{42,43} Albuminuria is common in chronic HF, as was shown in several studies.^{43–46} Approximately, one-third of patients had microalbuminuria, while 10% had macro-albuminuria. None of the investigated drugs in the large trials (candesartan, rosuvastatin, or aliskiren) showed an effect on albuminuria levels. In one small study in HFPEF, albuminuria was prevalent and associated with right and left ventricular dysfunction.⁴⁷

Prognostic properties

Data on the prognostic value of proteinuria/albuminuria are restricted to the same studies. In both Candesartan in HF Assessment of Reduction in Mortality and Morbidity (CHARM) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-HF (GISSI-HF) analyses, there was a stepwise increase in event rates from normo to micro and macro-albuminuria, independent of established risk factors.^{43,44} Albuminuria showed independent prognostic value on top of GFR and markers of tubular damage in another analysis from GISSI-HF.⁴⁸ In HFPEF, very few data exist, but suggest that indeed, albuminuria is associated with worse outcomes in these HF patients, either assessed by conventional urinary albumin excretion, or urine dipstick testing as was done in the Chronic HF Analysis and Registry in the Tohoku District 2 (CHART-2) study, where this method showed additional prognostic value on top of GFR^{46,47} (see Supplementary material online, Table S3).

Therapeutic implications

In renal disease and in hypertension, proteinuria is a strong target for therapy, but in HF no evidence exists to support tailoring therapy on proteinuria or albuminuria.

Markers of tubular damage and injury

Chronic renal hypoxia is the hallmark of end-stage renal disease, and since tubules are the most oxygen consuming parts of the kidney,

tubular dysfunction and damage frequently develops. Especially in a condition characterized by reduced tissue perfusion and hypoxia such as HF, the kidneys are prone to tubulointerstitial damage. Only limited histological data exist to actually support tubular injury and fibrosis in HF, let alone data on tubular function which is even harder to determine.⁴⁹ As a surrogate of tubular dysfunction, several markers that have shown strong associations with histological and functional damage in nephrology have been evaluated in HF. Some of these markers appear in urine since they are produced in the tubules and exert their action on the luminal side of the tubule, while others are (also) found in plasma.

Neutrophil gelatinase-associated lipocalin

Diagnostic properties

Neutrophil gelatinase-associated lipocalin (NGAL) is a small molecule from the lipocalin family. Neutrophil gelatinase-associated lipocalin complexes can exist in different forms (monomeric and dimeric) and different dimeric forms exist in plasma and urine following ischaemic injury.^{50,51} In AKI, urine and plasma levels of NGAL can rise 1000-fold or more in a short period of time, making it a strong diagnostic marker.⁵² Data are scarce on the relationship between urinary and plasma NGAL, but the two appear not to be closely related. Plasma NGAL is strongly related to infection and inflammation, and is slightly elevated in chronic disease. Urinary NGAL is thought to predominantly result from tubular production and secretion. For the diagnostic properties in AKI, both pools of NGAL are elevated; however, in HF, there is paucity of combined data.^{50,53} Most studies in acute HF on the diagnostic properties of NGAL to predict WRF (or termed AKI) have evaluated serum or plasma NGAL and the cohorts were small (see Supplementary material online, Table S4). In acute HF, serum NGAL levels are generally higher in patients who develop WRF than in those who do not, whereas urine NGAL levels were not elevated in patients with WRF.^{54,55} In chronic HF, plasma NGAL levels are associated with markers of renal function, including serum creatinine, Cystatin C, and eGFR.^{56–59} In GISSI-HF, urinary NGAL was assessed in over 2000 chronic HF patients but was found not to be an independent predictor of WRF, in contrast to both eGFR and urine kidney injury molecule-1 (KIM-1).⁴⁸ Finally, both plasma and urine NGAL levels were not affected by modulation of diuretic therapy in chronic HF, while both KIM-1 and N-acetyl- β -D-glucosaminidase (NAG) levels changed.⁶⁰

Prognostic properties

In acute HF, Maisel *et al.*⁶¹ showed in 186 patients the prognostic capabilities of plasma NGAL, where NGAL outperformed brain natriuretic peptide (BNP) and eGFR, and showed additive prognostic value on top of BNP levels. Similar results were later reported by Alvelos *et al.*⁶² Plasma NGAL levels also predicted mortality on top of eGFR or Cystatin C in 562 patients after hospitalization for HF.⁵⁹ In chronic HF, strong evidence for the prognostic value of plasma NGAL comes from the large Controlled Rosuvastatin in Multinational Trial in HF (CORONA).⁶³ In that study, plasma NGAL levels were not independent predictors of clinical events after adjustment for N-terminal brain natriuretic peptide (NTproBNP), C-reactive protein, and eGFR. Urinary NGAL levels were also not

associated with outcome in a small study in chronic HF.⁶⁴ However, most compelling evidence comes from the large GISSI-HF analysis, where urinary NGAL predicted all-cause mortality, but not HF hospitalization.⁴⁸ Therefore, both plasma and urine NGAL levels in HF appear to associate primarily with all-cause mortality, rather than HF hospitalizations.

Therapeutic implications

To date, no study evaluated NGAL-based therapies in HF, and most studies were retrospective. One interesting aspect is the fact that in an ischaemia-reperfusion animal model, administration of NGAL ameliorated tubulointerstitial damage.⁶⁵ This may suggest that in the future, NGAL could serve as therapeutic agent itself, rather than a marker for therapy guidance.

Kidney injury molecule 1

Diagnostic properties

Kidney injury molecule 1 is a protein that is found abundantly in the luminal side of the tubule. Its precise function is unknown, but elevated urinary KIM-1 levels are associated with HF hospitalization in the general population.^{66,67} During experimental and human renal injury, urinary KIM-1 levels are increased, and associated with histopathological evidence of tubulointerstitial damage, fibrosis, and inflammation.⁶⁷ Urinary KIM-1 levels were found to be two-fold increased in chronic HF compared with controls⁶⁴ and were found to be associated with ejection fraction, NYHA-class, and NTproBNP.⁶⁸ In GISSI-HF, urinary KIM-1 levels, together with low eGFR, predicted increased risk of WRF in chronic HF.⁶⁹ Data on KIM-1 in acute HF are restricted to two small studies, which have not yielded conclusive results^{70,71} (see Supplementary material online, Table S5).

Prognostic properties

In 150 patients with chronic HF, urinary KIM-1 levels showed an association with mortality and HF hospitalizations.⁶⁸ However, in the much larger GISSI-HF analysis, urinary KIM-1 was only marginally associated with clinical outcome.⁴⁸

Therapeutic implications

The possible therapeutic use of KIM-1 was shown in a study, where diuretics were discontinued and reinitiated.⁶⁰ Although serum creatinine did not change, urinary KIM-1 levels showed significant increases with discontinuation, and decreases with reinstatement of loop diuretics, suggesting that KIM-1 is sensitive to small haemodynamic and renal alterations. However, the study was small and these findings must be replicated in larger prospective studies.

N-Acetyl- β -D-glucosaminidase

Diagnostic properties

N-Acetyl- β -D-glucosaminidase is another marker of proximal tubular injury and has been investigated extensively in CKD and coronary artery disease.⁴² In acute HF, NAG levels were not elevated in patients who developed WRF and were not useful in determining risk of WRF (AUC 0.46).⁷¹ In chronic HF, NAG levels showed moderate associations with eGFR, RBF, and NTproBNP.⁶⁴ In GISSI-HF, NAG levels were strong univariate predictors of WRF over time, but

NAG was less useful than KIM-1⁶⁹ (see Supplementary material online, *Table S6*).

Prognostic properties

Jungbauer et al.⁶⁸ showed that NAG and KIM-1 were predictors of clinical events in chronic HF, although no multivariate analysis was carried out. In chronic HF, NAG was found to provide independent prognostic information on top of eGFR, but not when also adjusted for other important covariates.⁶⁴ Finally, NAG was an independent predictor of both all-cause mortality and HF hospitalization in GISSI-HF on top of both eGFR and albuminuria.⁴⁸

Therapeutic implications

No studies evaluated NAG levels-based guidance of therapies. In a small study, NAG levels showed similar sensitivity to diuretic discontinuation and reinitiation as KIM-1.⁶⁰

β -2-Microglobulin

Diagnostic properties

β -2-Microglobulin is a small molecule that has complete glomerular filtration and tubular reabsorption. This implies that when tubular dysfunction or injury occurs, urinary β -2-microglobulin appears in urine. Therefore, it has been evaluated as marker of renal deterioration and was associated with renal function decline in the general population and kidney donors.^{72,73} Data on the diagnostic properties of β -2-microglobulin to assess WRF are lacking (see Supplementary material online, *Table S7*).

Prognostic properties

Only few data are available on serum or urine β -2-microglobulin levels and outcome in HF. In 131 acute HF patients, serum β -2-microglobulin levels were strong predictors of cardiac events, including cardiovascular mortality.⁷⁴ In chronic HF, urinary β -2-microglobulin levels normalized for urinary creatinine were higher in patients with evidence of renal tubular damage and in anemia.⁷⁵ In two analyses from the same Japanese population, higher beta-2-microglobulin levels were associated with cardiac events, independent of baseline renal function.^{75,76}

Therapeutic implications

There are no data on therapeutic use of this marker in HF.

Fatty acid binding proteins

Diagnostic properties

Fatty acid-binding proteins (FABPs) are thought to play part in regulating energy metabolism in renal tubules. Different types exist, including liver type FABP (L-FABP) and heart type FABP (H-FABP) although these proteins are not only found in these tissues. In fact, L-FABP has been found in the proximal tubules after oxidative stress, while H-FABP may be found in distal tubules.⁷⁷ Heart type FABP levels are also thought to be released by damaged myocardium, thus being a marker in HF. As diagnostic marker of HF, H-FABP improved the diagnostic accuracy of NTproBNP, although the improvement was limited.⁷⁸ In a recent Japanese study in acute HF, serum H-FABP levels were shown to predict the occurrence of

WRF/AKI (AUC 0.79), outperforming urinary NAG, NGAL, and urinary L-FABP⁷⁹ (see Supplementary material online, *Table S8*).

Prognostic properties

In the aforementioned study, serum H-FABP levels were independent predictors of 90-day mortality, providing prognostic information on top of WRF.⁷⁹ In a similar study, higher H-FABP levels were associated with clinical outcome, including HF hospitalizations.⁷⁸ In chronic HF, persistently high-serum H-FABP levels were associated with the poorest outcome.⁸⁰

Therapeutic implications

There are no studies with FABPs-based treatment effects.

Urinary natriuretic peptides

Diagnostic properties

Natriuretic peptides are important in the management of HF, and may be used to guide therapy. Although they are not a renal biomarker, natriuretic peptides not only exert action in the kidney, promoting sodium and water excretion, but also appear into urine. Of particular interest is C type natriuretic peptide (CNP) that is mainly produced in the kidney and is thought to have anti-proliferative, anti-fibrotic, and possible vasodilatory properties. In acute HF, urinary CNP levels are elevated (*Figure 2*).⁸¹

Prognostic properties

In analysis from that study in acute HF, NT-CNP levels were strongly related to clinical outcome, independent of plasma NTproBNP⁸¹ (see Supplementary material online, *Table S9*).

Therapeutic implications

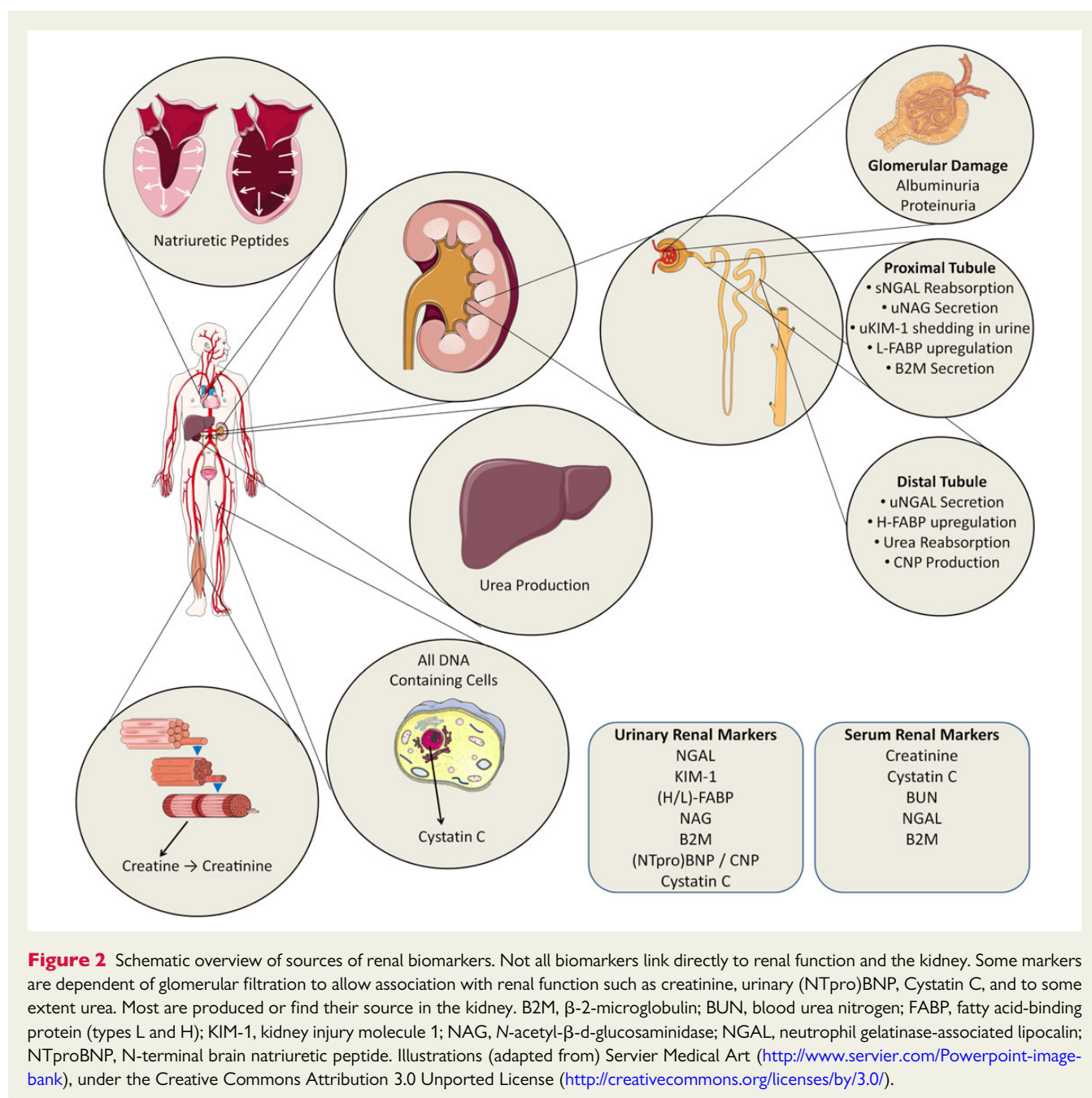
No data exist on therapy adjustment based on urinary natriuretic peptides.

Other markers

There are many more markers that have been associated with renal function or WRF in HF. Among those are pro-enkephalin (pro-ENK), interleukin 18 (IL-18), osteopontin, Galectin-3, and Growth differentiating factor-15 (GDF-15). The individual evidence is too weak to discuss each marker separately.

Enkephalins are small endogenous opioid peptides, but both enkephalin and enkephalin receptors are also highly expressed outside the nervous system, including the kidney.⁸² Owing to the instability of enkephalins, a stable fragment of their precursor, termed pro-ENK, has been devised as stable and reliable surrogate plasma marker.⁸³ In patients with AKI after cardiac surgery, pro-ENK was shown to rapidly increase.⁸⁴ In acute myocardial infarction, increased pro-ENK was associated with renal dysfunction and predicts major cardiac events.⁸⁵ Pro-ENK is a dynamic marker, and levels can significantly change within one day. Larger studies are currently ongoing to validate these findings, also in HF (*Figure 3*).

Interleukin 18 shows diagnostic capabilities in nephrology, where IL-18 predicts AKI. In HF, evidence is scarce, and suggests only modest diagnostic capabilities to predict WRF.⁸⁶ Osteopontin is a



glycoprotein that appears to be involved in fibrosis and extracellular matrix remodelling. It shows a modest association with renal function in HF, and may show have value in HF although its association with WRF is unknown.⁸⁷ Galectin-3 is a molecule that is thought to be involved in the stiffening of extracellular matrix, causing (myocardial) fibrosis. Galectin-3 levels are increased in acute and chronic HF and are associated with renal function.^{88,89} Similar to urinary natriuretic peptide, even in the presence of high galectin-3 in plasma, only limited amounts of galectin-3 appear into urine, suggesting tubular handling.⁹⁰ Overall, the role of galectin-3 as a renal biomarker in HF is unclear.

Growth differentiating factor-15 is a member of the transforming growth factor family of proteins that are involved in tissue

repair and remodelling. It has been shown to provide additional prognostic information in HF, and changes in GDF-15 levels have been associated with changes in eGFR, but studies assessing possible therapeutic consequences of measuring GDF-15 are still ongoing.⁹¹

Summary and clinical implications

Renal dysfunction is one of the key features of HF, and guidelines recommend thorough monitoring of renal function.²⁴ However, the optimal technique to evaluate renal function is unclear, and there is no consensus on which parts of renal function (GFR, albuminuria, tubular damage) should be evaluated. There is difficulty in

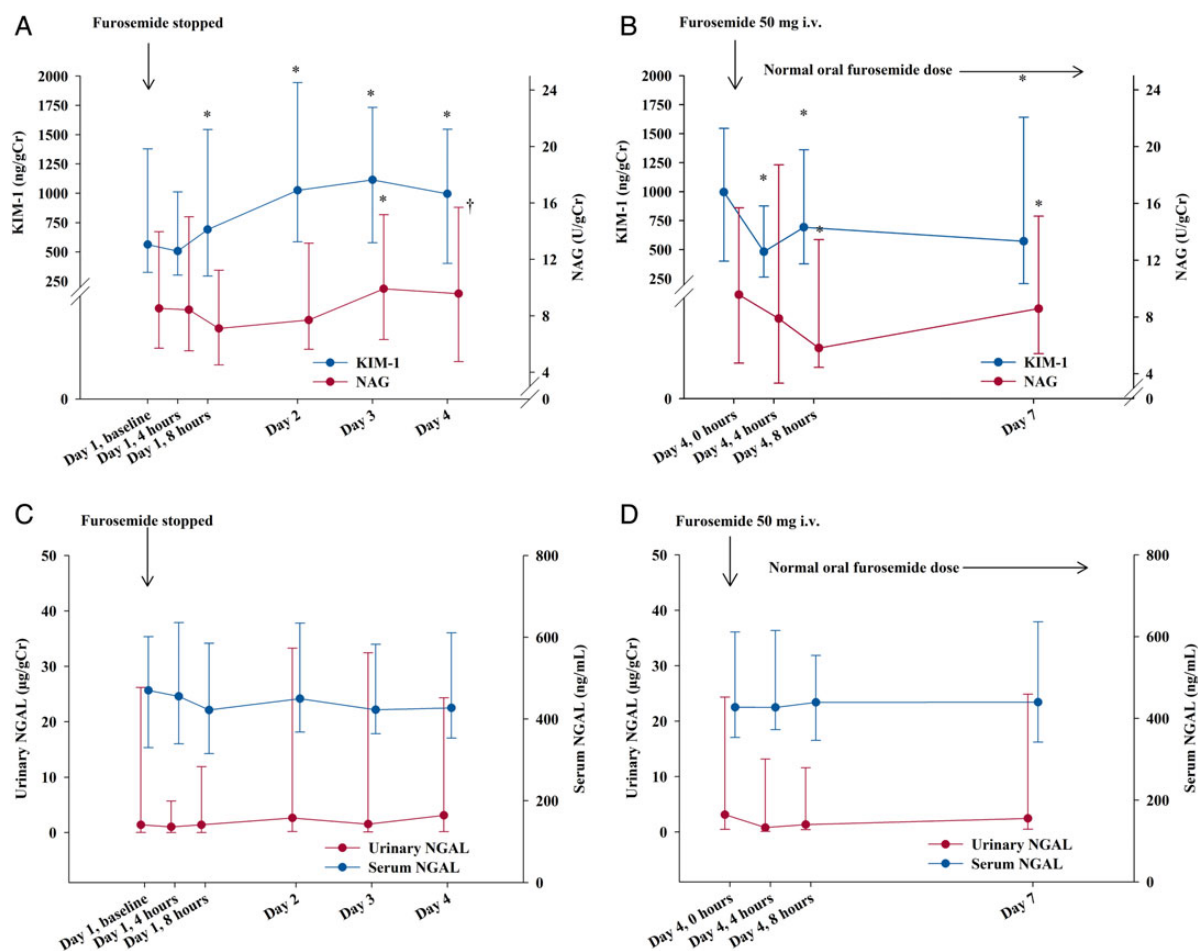


Figure 3 Example of renal biomarkers in response to alteration of heart failure therapy. This figure illustrates possible effect of treatment alterations on renal biomarkers. Specifically, in this study, 30 presumed euvolemic chronic HF patients on diuretic therapy discontinued diuretics. After 4 days, diuretics were reinitiated (starting with a bolus infusion). During diuretic withdrawal, serum creatinine did not change while natriuretic peptides and urinary creatinine increased. Both urinary KIM-1 and NAG were susceptible to these changes, and showed increased urinary levels. This effect was completely reversed with the reinitiation of diuretics. Neither serum nor urinary NGAL levels changed significantly during the study. HF, heart failure; KIM-1, kidney injury molecule 1; NAG, N-acetyl- β -D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin. Reprinted from Damman et al.⁶⁰ with permission from Elsevier.

translating the information of renal biomarkers into changes in therapy, although clinicians use markers of renal function in HF patients every day. They are used to evaluate cardiovascular risk, assess haemodynamic status, or are used to select adequate dosing of evidence-based treatments. As such, markers of renal function have become a necessity, and it is unthinkable to assess a patient with HF without measuring creatinine or BUN, and estimating GFR. However, as reviewed in the current paper, evidence to support HF treatment guided on these markers is lacking (Table 1). On the other hand, risk associated with renal injury or dysfunction is clear, and it seems logical that interventions that lead to better renal function should translate into better outcomes. Unfortunately, with novel renal biomarkers, there is a paucity of data on biomarker-guided treatment. At this moment, measurement of (novel) renal biomarkers may help to determine cardiovascular risk, but there

is no role (yet) for these biomarkers to change therapy to improve clinical outcome in HF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

D.J.V.V. and K.D.: conceived and designed the research and drafted the manuscript. L.M.R. and A.S.M.: made critical revision of the manuscript for key intellectual content.

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Table 1 Characteristics of renal markers

Marker	Epidemiology		Diagnostic Capabilities for AKI/WRF		Prognostic Information		Therapeutic Implication	
	AHF	CHF	AHF	CHF	AHF	CHF	AHF	CHF
Serum Creatinine	↑↑↑	↑↑	+	+	+++	+++	+/?	+/?
Serum Cystatin C	↑↑↑	↑↑	?	?	+++	+++	-/?	-/?
Blood urea nitrogen	↑↑↑	↑↑	?	?	++++	++++	+/?	+/?
Albuminuria	++/?	++	?	+	+/?	+++	-/?	-/?
Serum NGAL	↑↑	↑	-	?	+	+	-/?	-/?
Urinary NGAL	↑↑	↑↑	+	+	?/+	+	-/?	-/?
Urinary KIM-1	↑↑/?	↑↑	-	+++	?	-	-/?	+/?
Urinary NAG	?	↑↑	-	+	?	+	-/?	+/?
Urinary/serum β2M	↑↑	↑↑	?	?	+	+	-/?	-/?
FABP	↑↑/?	↑↑/?	+	?	+	+	-/?	-/?
Urinary NP	↑↑	↑	?	?	+	+	-/?	-/?

Arrows indicate increased levels, and to what extent. Plus and minus signs indicate the presence or absence of characteristics, and to what extent. Stronger colours indicate stronger associations. Prognostic information was evaluated as significant association with clinically relevant endpoints such as mortality, heart failure hospitalization, or a combined cardiovascular endpoint which was different in each individual study.

AHF, acute heart failure; AKI, acute kidney injury; β2M, beta-2-microglobulin; BUN, blood urea nitrogen; CHF, chronic heart failure; FABP, fatty acid-binding protein (types L and H); KIM-1, kidney injury molecule 1; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NP, natriuretic peptide; WRF, worsening renal function.

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