Current and novel renal biomarkers in heart failure

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Abstract Renal function is the most important predictor of clinical outcome in heart failure (HF). It is therefore essential to have accurate and reliable measurement of renal function and early specific markers of renal impairment in patients with HF. Several renal functional entities exist, including glomerular filtration (GFR), glomerular permeability, tubulointerstitial damage, and endocrine function. Different markers have been studied that can be used to determine changes and the effect of treatment in these entities. In the present review, we summarize current and novel markers that give an assessment of renal function and prognosis in the setting of acute and chronic HF.

Introduction

In patients with heart failure (HF), impaired renal function is often present and one of the strongest predictors of clinical outcome [1–4]. Both worsening renal function (WRF) and acute kidney injury (AKI) are prevalent in patients with acute and chronic HF and are associated with an increased mortality and morbidity [1, 5, 6]. In addition, renal dysfunction might not only be a marker of a poor clinical condition, but might also contribute to the development and progression of heart failure [7]. Renal function and changes in renal function therefore provide important clinical information in patients with HF.

Usually, “renal function” is defined as the filtration ability of the kidney, which can be expressed as the glomerular filtration rate (GFR). Creatinine and empirical formulas that are mainly based on creatinine are used to estimate GFR in patients with HF [8]. However, GFR does not cover the entire function of the kidney, which also comprises of glomerular permeability, tubular function, and several specific functions such as vitamin D metabolism and erythropoietin production. Therefore, several markers other than creatinine can be used to estimate various functions of the kidney.

In the present review, we summarize current and novel promising markers/ways to assess renal function and changes in renal function in patients with HF and their prognostic potential in HF. We will focus on glomerular function, glomerular permeability, and tubulointerstitial damage. Table 1 gives an overview of the clinical characteristics of the markers that will be discussed in the present review.

Glomerular filtration rate

The golden standard of measuring GFR is by specific markers such as iothalamate or inulin clearance. These
measurements are, however, patient-unfriendly, time-consuming and expensive and can, therefore, not be used in daily clinical practice. In study cohorts, these techniques have been used to validate easier estimations of GFR, mostly in patients with chronic HF [8, 9]. Instead, different markers that give an estimate of GFR are used as surrogate markers for GFR.

**Serum creatinine**

Creatinine is a break down product of creatine phosphate, which is normally formed at a constant rate in the skeletal muscles. Upon presentation in the plasma, it is freely filtered through the glomerulus and appears in the urine. Creatinine is, however, also actively secreted in the tubules and accordingly its clearance overestimates true GFR to a varying extent [10].

Increased serum creatinine is a common finding in patients with acute and chronic HF and is a sign of renal impairment. In large cohort studies and substudies of randomized clinical trials, an increased serum creatinine level was strongly associated with impaired clinical outcome [11, 12]. However, serum creatinine levels are prone to bias due to several shortcomings. First, the production of creatine phosphate is not constant. Due to changes in muscle

| Table 1 Properties of different markers |
|----------------------------------------|
| Detection | “Validation” | Relation with prognosis | Pro’s | Cons |
|------------|--------------|--------------------------|-------|------|
| **Glomerular filtration rate**          |              |                          |       |      |
| Creatinine | Serum \(^a\) | CHF                      | Strong evidence | Easy | Exponential relationship with GFR |
|            | AHF          |                          |        | Cheap| Dependent on muscle mass         |
| (s)MDRD    | Serum        | CHF                      | Strong evidence | Valid| Formula (calculation)          |
|            | Not in AHF   |                          |        | Accurate| Less reliable in extremes of GFR |
| BUN        | Serum        | CHF                      | Emerging evidence | Easy | Interpretation difficult |
|            | AHF          |                          |        | Cheap |                              |
| Cystatin C | Serum \(^a\) | CHF                      | Evidence in AHF | Unbiased | Interpretation difficult |
|            | AHF          |                          |        | Very reliable | Costs |
| **Glomerular permeability**             |              |                          |       |      |
| Albuminuria | Urine      | CHF                      | Strong evidence CHF | Easy obtainable | Low specificity |
|            | Not in AHF   |                          |        | Cheap | Additive to GFR                  |
| **Tubulointerstitial damage**           |              |                          |       |      |
| NAG        | Urine        | CHF                      | Emerging evidence CHF | Easy obtainable | Low specificity |
|            | Not in AHF   |                          |        | Additive to GFR and UAE | Costs |
| KIM-1      | Urine        | CHF                      | Emerging evidence CHF | Easy obtainable | Strong marker of AKI |
|            | Not in AHF   |                          |        | Additive to GFR and UAE | Costs |
| NGAL       | Urine/ Serum | CHF                      | Emerging evidence CHF and AHF | Easy obtainable | Low specificity especially in serum |
|            | AHF          |                          |        | Additive to GFR and UAE | and in CHF |
| IL-18      | Urine/ Serum | CHF                      | Emerging evidence CHF | Easy obtainable | Strong marker of AKI |
|            | Not in AHF   |                          |        | Strong marker of AKI | Also strongly increased |
|            | Not in CHF   | None                     |        | Elevated in sepsis | in inflammation |
| FABP-1     | Urine/ Serum | Not in CHF               | None   | Strong marker of AKI | Also found in liver |
|            | Not in AHF   |                          |        |     |

\(^a\) Can be measured in urine, but then does not resemble GFR

AHF acute heart failure, AKI acute kidney injury, BUN blood urea nitrogen, CHF chronic heart failure, FABP fatty acid binding protein, GFR glomerular filtration rate, IL-18 Interleukin 18, KIM-1 kidney injury molecule 1, MDRD modification of diet in renal disease (formula), NAG \(\text{N}\)-acetyl-beta-D-glucosaminidase, NGAL neutrophil gelatinase-associated lipocalin, UAE urinary albumin excretion.
Estimated GFR, creatinine-based formulas

To overcome the problems that may arise with the use of serum creatinine or creatinine clearance, as an estimate of GFR, large (sub) studies have generated empirical formulas that give a more reliable estimation of GFR based on serum creatinine [13]. In addition to serum creatinine, they typically include age and gender, and sometimes weight, race, blood urea nitrogen, and albumin. The most common formulas are the Cockcroft-Gault equation, which is an estimate of creatinine clearance, and the currently widely used (simplified) Modification of Diet in Renal Disease (sMDRD/MDRD) formulas [13]. These formulas have been validated in renal disease, and give a reasonably accurate estimation of GFR, especially in patients with chronic kidney disease and renal function impairment. More recently, these formulas have been validated in patients with chronic HF [8]. Smilde et al. showed that in patients with relatively preserved renal function, the 6-variable MDRD formula showed the most accurate estimation of GFR, with similar prognostic information compared to real GFR [8]. However, all formulas, including Cockcroft-Gault and (s)MDRD overestimate real GFR in the lower levels of true GFR and underestimated real

![Fig. 1](image-url)  
**Fig. 1** Relationship between serum creatinine and estimated GFR: effect of change in serum creatinine. Different changes in estimated GFR with similar changes in serum creatinine. A pronounced decrease in GFR from normal—the flat part of the curve—gives just a subtle increase in serum creatinine that often stays within the normal day-to-day variability of the assay and, therefore, may go unnoticed. The other way round, a trivial further decrease in already compromised GFR leads to a steep rise of creatinine, based on the steepness of the curve here, that can lead to undue concern. For example, a decrease in serum creatinine from point A to B results in a decrease in eGFR of 15 ml/min/1.73 m². However, a decrease in serum creatinine from point B to C results in a much more pronounced decrease in eGFR of 75 ml/min/1.73 m². Depicted is the GFR estimated by the simplified MDRD for a 70-year-old white male.
GFR in the higher levels of true GFR. Accordingly, in clinical practice, when GFR decreases over a longer period of time, the decrease will be underestimated by these equations. Nevertheless, in numerous studies, both acute and CHF showed that GFR as estimated by these formulas (mostly sMDRD) is an important prognostic factor [2, 8, 16, 17]. Recently, to account for the poor performance of the MDRD equation in the (near) normal and higher ranges of GFR, a new equation, the CKD-EPI equation was developed. It is now considered the preferred estimate of GFR in renal disease. This formula is similar to the MDRD but has creatinine-dependent gender differences and generates higher eGFR at lower creatinine levels. It has a better performance in subjects with normal or near-normal renal function, but this equation has not yet been validated in HF [18]. Given the fact that invasive determination of GFR is expensive and time consuming, to date, the MDRD formula is currently considered the golden standard of estimation of GFR in clinical practice.

Blood urea nitrogen (BUN)

BUN, a waste product of protein catabolism, has been extensively studied in dialysis patients and is an important target for removal by (hemo) dialysis, as well as a marker for the effectiveness of dialysis. Although most clinicians will use BUN with or without serum creatinine in daily practice, only in recent years, the relationship of BUN with outcome in cohorts of patients with HF has been established (Table 2). In large cohorts of patients with acute and chronic HF, an elevated BUN has been shown to be a strong predictor of morbidity and mortality [19–26]. BUN was an even better predictor of outcome compared to GFR in the OPTIME-CHF population [27]. It has been argued that BUN is much more than a reflection of GFR [28]. It is also largely dependent on protein intake, catabolism, and tubular reabsorption. The latter is coupled to sodium reabsorption and may, therefore, reflect the extent of forward failure. Together, BUN or urea may be a reflection of both GFR and of the severity of HF, whereas there is also clear cut impact of nutritional status and catabolic state. This may be the reason why it possesses strong predictive abilities, but in terms of estimation of renal function, and the effect of possible treatment on renal function, BUN may be a more varying and, therefore, unreliable marker compared to creatinine and creatinine-based formulas.

Cystatin C

Of all markers that give an estimate of GFR, cystatin C is the newest, although first reports on cystatin C were already published 30 years ago. Cystatin C is freely filtered through the glomerulus and completely reabsorbed and degraded in the tubulus. Its level in the circulation is therefore an ideal marker of GFR [29]. Cystatin C has been shown to be superior to serum creatinine as an estimate of GFR in several different patient populations, in particular, in the near-normal, normal and higher range, where creatinine-derived measures perform poorly [30]. It is a strong predictor of outcome in coronary artery disease, diabetes, but also the general (elderly) population [31–33]. Data on cystatin C in chronic and acute HF are scarce, but some studies have shown the prognostic power of cystatin C in CHF [33, 34]. In acute HF, cystatin C showed independent prognostic information, even in patients with normal serum creatinine [35].

However, in HF, no data exist on the reliability of cystatin C to accurately estimate GFR. In renal disease, cystatin C has been shown to provide a reliable and less biased estimate of GFR compared to serum creatinine [36–38]. Cystatin C is not influenced by body mass, muscle turnover, and cachexia, which are important confounders of serum creatinine [39]. There have been concerns that cystatin C may be dependent on inflammatory status or smoking, but others have reported no bias by these factors [32, 40, 41]. Cystatin C levels may be used alone or in a formula similar to creatinine-based formulas, but in each circumstance give accurate estimation of GFR, although

### Table 2 Relationship between blood urea nitrogen and outcome in heart failure studies

| Study       | Year | N     | Setting | BUN (mg/dL) | Relative risk for mortality |
|-------------|------|-------|---------|-------------|-----------------------------|
| Lee [25]    | 2003 | 4031  | ADHF    | 29 ± 19     | 1.49 (1.39–1.60) per 10 units increase |
| Aronson [19]| 2004 | 541   | ADHF    | 34 ± 22     | 2.3 (1.3–4.1) for quartiles  |
| Heywood [24]| 2005 | 680   | CHF     | 29 ± 20     | BUN 30–50: 1.9, BUN >50: 2.2 |
| Shenkmman [26]| 2007 | 257   | ADHF    | 33 ± 22     | 3.6 (1.8–7.3) per log unit increase |
| Filippatos [21]| 2007 | 302   | ADHF    | 31 ± 17     | 1.03 (1.00–1.05) per unit increase |
| Cauthen [20]| 2008 | 444   | CHF     | 14 (6–22)   | 1.04 (1.03–1.06) per unit increase |
| Klein [27]  | 2008 | 949   | CHF     | 25 (14–41)  | 1.11 (1.07–1.15) per 5 units increase |
| Lin [22]    | 2009 | 243   | CHF     | 27 ± 17     | 1.24 (1.02–1.51) for BUN-to-creatinine ratio |
| Gotszman [23]| 2010 | 362   | ADHF    | 23 (17–29)  | 1.80 (1.30–2.49), per tertile BUN/creatinine |

ADHF Acute decompensated heart failure, BUN Blood urea nitrogen, CHF Chronic heart failure

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not always superior to creatinine [36, 38]. Whether cystatin C may give more reliable estimations of changes in GFR compared to serum creatinine is unknown. From a physiological perspective, given the totally free filtration through the glomerulus and total degradation in the tubules, it is likely that it may be a more accurate marker of changes in renal function compared to creatinine [39].

Although cystatin C seems to be superior to creatinine in estimating GFR and may be at least identical to creatinine in establishing prognosis, it is far understudy in clinical practice. There are two important reasons and disadvantages of cystatin C to explain this. First, serum creatinine has been around for such a long time that clinicians are familiar with its normal values and in most instances can adequately estimate GFR for a particular patient with a certain serum creatinine. For cystatin C, however, there is so little experience that only few will know what GFR accompanies each cystatin C level. Secondly, as cystatin C is not routinely measured, cystatin C measurement is relatively expensive, especially if it should replace creatinine as a (daily) assessment of renal function [42]. On the other hand, several other markers that have comparable or more expensive costs to determine have made it into clinical practice in cardiology, including Troponins and N-terminal brain natriuretic peptide. It will therefore take a change of mind from clinicians and researchers to eventually replace serum creatinine with cystatin C in clinical practice, once future studies will provide more solid information on its routine use as point estimate and measure of changes in GFR.

Glomerular permeability

The previously mentioned markers give an estimate of GFR, the ability of the kidney to clear a certain amount of blood from the waste substances of metabolism. However, besides a reduction in filtration capabilities or even in the presence of preserved GFR, glomerular leakage may develop when glomerular capillary damage occurs. In these circumstances, larger than normal molecules enter the ultrafiltrate of which albumin is the most important one. When the leakage of albumin exceeds the tubular capacity of reabsorption, it appears in the urine in abnormal amounts.

Albuminuria

In patients with diabetes, hypertension, and chronic kidney disease, micro (30–300 mg/gram creatinine) and macroalbuminuria (>300 mg/gram creatinine) are commonly observed [43–45]. Importantly, albuminuria has been advocated as an important therapeutic target in patients with chronic kidney disease. Even independent of blood pressure, albuminuria is considered to be an important target for therapy, although strong evidence to support this is lacking. Even so, in CKD patients with diabetes, the degree of reduction in albuminuria was strongly correlated with cardiovascular outcome and, more importantly, incident HF [46]. The pathophysiology of albuminuria in general is considered to be related to endothelial dysfunction, increased intraglomerular pressure, and atherosclerosis [47]. Importantly, its pathophysiology, therefore, differs considerably from that of decreased GFR [48]. On the other hand, there are suggestions that albuminuria in HF may be associated with impaired renal perfusion and increased venous congestion, in analogy to decreased GFR [49–53]. These two entities define the clinical syndrome of HF, and therefore, it is surprising that only recently data on the prevalence and prognostic information on albuminuria and proteinuria in HF has been published. Van der Wal et al. were the first to show that albuminuria was present in 32% of patients with HF, compared with 10% of an age and gender-matched healthy population [54]. In large sub studies of the CHARM and GISSI-HF trial, micro and macro-albuminuria were not only prevalent, but also associated with a strongly increased mortality rate [55, 56]. This was even apparent in patients without decreased GFR, which may suggest that either albuminuria may be a very early sign of renal damage/insufficiency as it has been reported in the general population, or that different mechanisms may contribute to reduced GFR and increased albumin excretion. For example, in general population studies, albuminuria was strongly related with the presence of diabetes and hypertension and might, therefore, be a reflection of comorbid organ dysfunction in HF [57]. These substudies assessed albuminuria in morning spot urine. In a substudy of the Val-HEFT, dipstick-positive proteinuria (rather than albuminuria) was infrequent, but still associated with impaired clinical outcome [58]. However, proteinuria as assessed by dipstick is a less precise, qualitative, rather than quantitative measurement and is therefore less sensitive and inaccurate estimate of high normal, micro or macroalbuminuria.

Importantly, both CHARM and GISSI-HF studies failed to show a significant reduction in albuminuria with either angiotensin receptor blockade or statin treatment. It is therefore unlikely that albuminuria may be useful as a primary target for therapy in patients with HF. However, albuminuria may serve as marker of prognosis in patients with HF and as a predictor of HF in patients without cardiac dysfunction, even when GFR is normal.

Tubulointerstitial damage

Nephrologists increasingly use markers that represent tubulointerstitial injury to provide a more appropriate estimation of “renal function”. Although most markers
have not made it into clinical practice yet, first results in HF patients look promising

*N*-acetyl-beta-d-glucosaminidase (NAG)

NAG is a lysosomal enzyme that is formed in the proximal tubule and shed into the urine in response to tubular injury. It has been extensively studied in experimental and clinical settings and is a sensitive marker of proximal tubular damage in renal disease, but also after cardiopulmonary bypass grafting and diabetic nephropathy [59–61]. NAG is a prominent predictor of the occurrence of AKI or WRF [60, 62]. In CHF, urinary NAG levels are strongly elevated compared to age and gender-matched controls [63]. Interestingly, lower renal blood flow was associated with elevated NAG levels, indicating that tubulointerstitial damage may develop as a result of decreased renal perfusion, potentially by a decreased cardiac output [63]. Furthermore, higher NAG levels were associated with poorer clinical outcome in this group of patients with HF, independent of GFR. On the other hand, higher levels of NAG are also found in various other conditions, such as urinary tract infections, which may limit specificity [64]. Therefore, future research is needed in both acute and chronic HF to further establish the place of NAG as a renal tubular marker.

Kidney injury molecule 1 (KIM-1)

KIM-1 is a transmembrane protein that cannot be found in urine in normal situations. However, after hypoxic tubular injury, proximal tubule epithelial cells express KIM-1 at extremely high levels, which can reach up to 1000-fold [65]. In experimental and clinical renal disease, KIM-1 urine levels reflect the extent of tubulointerstitial levels [66]. KIM-1 expression in biopsies of renal tissues in response to tubulointerstitial damage is primarily located at the proximal tubular epithelial cells and is predominantly present in areas of early fibrosis [67]. In children undergoing cardiopulmonary bypass grafting, KIM-1 was superior to NAG in predicting the occurrence of AKI after surgery [68]. The increase in both markers occurred almost 24 h before a rise in serum creatinine was apparent. KIM-1 (and NAG) may, therefore, possess properties related to the extent of (chronic) tubulointerstitial damage, but may also accurately and early predict those patients that are at increased risk of developing a deterioration in renal function. Urinary KIM-1 levels decrease in response to anti-hypertensive treatment with a combination of either thiazides, a low salt diet or angiotensin receptor blockade, and the reduction in KIM-1 was correlated with a reduction in proteinuria [69]. Of note, in animal experiments, the changes in urinary levels of KIM-1 during renoprotective intervention reflected the changes in tubulointerstitial KIM-1 expression, suggesting that changes in urinary KIM-1 levels will have the potential to monitor the course and response to the intervention of tubulointerstitial damage [70]. As discussed earlier, albuminuria may also exist in chronic HF. Higher protein loading of the tubule may have a direct damaging effect on the tubular epithelium [69]. This can, therefore, be a different pathophysiologic pathway by which tubular damage and thereby higher urinary KIM-1 expression may develop. Clinical data on KIM-1 expression in chronic HF is limited. We recently found that urinary KIM-1 levels were strongly increased in patients with stable chronic HF and only mildly impaired GFR [63]. In fact, even in patients with normal GFR, urinary KIM-1 levels were strongly increased in comparison with matched control [63]. Importantly, urinary KIM-1 levels at a single point in time predicted outcome in these patients, independent of GFR. These results further acknowledge the prevalence and prognostic importance of tubulointerstitial damage in chronic HF and the ability of KIM-1 to identify high risk individuals. To date, no study evaluated KIM-1 expression in the setting of acute (decompensated) HF or evaluated the ability of KIM-1 to predict worsening of renal function in HF. As KIM-1 is predominantly expressed in response to ischemic tubular damage, especially the setting of acute HF, KIM-1 may be of clinical importance in this setting, although studies are still lacking. Although urinary KIM-1 is highly sensitive to (proximal) tubulointerstitial damage, it lacks specificity in the presence of other (chronic) comorbid organ dysfunction. For instance, KIM-1 levels are also increased in patients with hypertension and diabetic nephropathy [67]. As these patients may have a high risk for the development of HF, the baseline expression of KIM-1 in urine may be biased in such conditions.

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a small (21kD) protein that is normally detectable in serum as it is secreted in low amounts in lung, kidney, trachea, stomach, and colon [71]. Because of its small molecular weight, it is freely filtered through the glomerulus and completely reabsorbed in the tubules [71]. NGAL can be measured in plasma or urine. In normal situations, urine and plasma levels are low. Plasma NGAL levels are less specific for (acute) renal disease, as higher levels are also found in inflammation, sepsis, or cancer [71]. Urine levels are much less affected by these situations, since the NGAL that appears in the urine is secreted only from the tubules (plasma NGAL is filtered and totally reabsorbed) [71, 72]. In AKI, both plasma and urine NGAL rise strongly, and therefore, the relative contribution of non-renal origins of NGAL is considered negligible. In response to tubulointerstitial damage, however, both serum
and urinary concentrations may rise up to a 1000-fold and high concentrations of NGAL are expressed in urine, which mostly comes from production in the distal nephron (loop of Henley and collecting ducts) [71–73]. Urinary NGAL may, therefore, reflect occurrence of ischemic tubular injury in more distal parts of the nephron. However, high levels of NGAL in urine (and serum) have also been observed during proximal tubular injury, indicating that the site-specific increase in NGAL may be more complex [74]. NGAL measurements may be clinically useful as higher levels of NGAL are prominent predictors of the occurrence of AKI or WRF. In a landmark paper, Mishra et al. showed that higher NGAL serum and urine levels were able to predict the occurrence of AKI with remarkable specificity and sensitivity [73]. Importantly, similar to KIM-1 and NAG, the rise in NGAL levels preceded the rise in serum creatinine by over 24 h. Interestingly, administration of NGAL in experimental setting of acute ischemic renal injury attenuated tubular injury, suggesting a possible therapeutic role for NGAL by protecting against tubulointerstitial injury by inducing re-epithelialization [75]. Recent reports have studied the relationship between NGAL and WRF on outcome in acute HF. Higher plasma NGAL levels were found to predict the occurrence of WRF in patients admitted with acute HF [76]. A different study showed that higher plasma NGAL levels were related to a poorer clinical outcome [77]. In chronic HF, urinary NGAL levels are strongly increased in comparison with matched controls [78]. However, NGAL levels did not predict outcome in this group of CHF patients, in contrast to both NAG and KIM-1 [63]. Considering the lack of specificity of NGAL in the setting of chronic instead of acute renal failure, the acute rather than the chronic HF patient population may be a more suitable setting for the clinical implementation of NGAL.

Interleukin 18 (IL-18)

IL-18 is a proinflammatory cytokine that is quickly and highly upregulated in response to AKI in various situations [79]. It is one of the many proinflammatory cytokines, but IL-18 is particularly interesting given it possible role in mediation of ischemic renal failure [80]. IL-18 is detectable in urine after AKI and a sensitive predictor of AKI in the setting of cardiopulmonary bypass grafting [80]. In a comparative analysis, IL-18 levels preceded the rise in creatinine, but the rise in IL-18 was slower compared to the rise in NGAL [80]. Importantly, as a proinflammatory cytokine, IL-18 levels are also strongly increased in inflammatory conditions, such as arthritis and sepsis [81]. This limits the specificity of IL-18 in the setting of mixed AKI and pronounced inflammation. Some studies have investigated the role of IL-18 as a proinflammatory cytokine in ischemic heart disease. In a small study, plasma IL-18 levels were increased in patients with HF, and those who survived had lower baseline plasma IL-18 levels [82]. Interestingly, this study found increased activity of IL-18 in human myocardium of failing hearts, which may suggest that IL-18 has pathophysiologic role in the setting of HF. IL-18 also predicts outcome in ischemic heart disease and, as such, was a predictor of the incidence of HF [83]. No studies have investigated the ability of IL-18 to predict AKI/WRF in the setting of HF.

Fatty acid-binding protein (FABP)

FABPs are proteins that bind selectively to free fatty acids. There are numerous different FABPs that have tissue-specific expression, which include the liver, heart, and brain [84]. Of these, liver FABP, (L-FABP or FABP-1) and heart FABP (H-FABP or FABP-3) have been associated with impaired renal function [85]. Both proteins are thought to play a role in the energy metabolism of the large amounts of energy consuming renal tubules. FABP-1 is exclusively found in the proximal tubules, whereas FABP-3 is localized in the distal tubules [86]. In response to ischemic injury, FABP-1 and FABP-3 are shed into the urine and detectable as sensitive and specific biomarkers of AKI. FABP-1 may even outperform NGAL and KIM-1 in AKI [87]. In an animal model, FABP-1 was superior to NAG in predicting AKI [39]. Further observations suggest that urinary FABP-1 levels are increased in response to hypoxia induced by impaired peritubular capillary blood flow in the kidney, a situation which is likely to exist in a low perfusion state such as HF [86]. FABP-3 levels may predict outcome in HF, but the ability to predict AKI has not yet been studied [88].

Conclusions

The interaction between heart failure and renal impairment is not static, but comprises of dynamic changes in volume status, inflammatory response, neurohormonal activation and changes in renal function, by natural course, or in relation to therapy. These changes may be quick and substantial, but may also be slow and subtle. Finding the right marker to predict renal function in all of these situations may be impossible, but new markers are emerging that seem to perform better than serum creatinine alone. Some of these markers may give a good representation of GFR, such as cystatin C, BUN, while others give information on glomerular permeability (albuminuria) or tubulointerstitial damage (NAG, KIM-1, NGAL, and FABP). Importantly, the latter group (including IL-18) represents markers that may also predict acute changes in renal function, even
before changes in creatinine occur. These markers are therefore suitable candidates as markers of treatment effect and as possible targets for therapy. New randomized clinical trials should, therefore, include measurement of these markers and possibly target these markers to preserve or even improve renal function in patients with HF.

**Conflicts of interest** DJVV reports having received consultancy fees from Biosite (Inverness Medical), manufacturer of NGAL test kits.

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