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**REVIEW**

*The heart and other organs*

# The role of the kidney in heart failure

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Renal dysfunction is common in patients with heart failure and is associated with high morbidity and mortality. Cardiac and renal dysfunction may worsen each other through multiple mechanisms such as fluid overload and increased venous pressure, hypo-perfusion, neurohormonal and inflammatory activation, and concomitant treatment. The interaction between cardiac and renal dysfunction may be critical for disease progression and prognosis. Renal dysfunction is conventionally defined by a reduced glomerular filtration rate, calculated from serum creatinine levels. This definition has limitations as serum creatinine is dependent on age, gender, muscle mass, volume status, and renal haemodynamics. Changes in serum creatinine related to treatment with diuretics or angiotensin-converting enzyme inhibitors are not necessarily associated with worse outcomes. New biomarkers might be of additional value to detect an early deterioration in renal function and to improve the prognostic assessment, but they need further validation. Thus, the evaluation of renal function in patients with heart failure is important as it may reflect their haemodynamic status and provide a better prognostic assessment. The prevention of renal dysfunction with new therapies might also improve outcomes although strong evidence is still lacking.

**Keywords** Heart failure • Chronic kidney disease • Cardio-renal syndrome • Acute kidney injury

## Introduction

The incidence of heart failure (HF) and chronic kidney disease (CKD) has been steadily increasing and will further increase due to ageing of the general population and better treatment of acute cardiac and renal diseases. Heart failure and CKD frequently co-exist, which can be related to common risk factors, e.g. hypertension, diabetes, and atherosclerosis, but also to common pathogenic mechanisms, such as the activation of the sympathetic nervous system, renin–angiotensin system, inflammation, and oxidative stress. Evidence also suggests that cardiac dysfunction may cause renal dysfunction, and vice versa. This current review discusses the role of the kidney in patients with HF. The definitions of CKD and acute kidney injury (AKI) are summarized in *Tables 1* and *2*.[1–4]

## Epidemiology and clinical significance of kidney disease in heart failure

### Prevalence and prognostic significance

Chronic kidney disease is present in ~30–40% of the patients with HF with a greater prevalence in those with more severe symptoms.[5–7] Multiple studies have shown worse outcomes in patients with concomitant CKD and HF. In a landmark analysis of 1906 patients, the estimated glomerular filtration rate (eGFR) was the most powerful predictor of mortality with a greater significance than the NYHA class and the left ventricular ejection fraction.[8] The strong and independent prognostic value of markers of renal function, such as serum creatinine, eGFR,

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**Table 1 Stages of chronic kidney disease**

| Stage[1,2] | Description | GFR (mL/min/1.73 m$^2$) | Albuminuria stages (ACR, mg/g) | | |
|---|---|---|---|---|---|
| | | | A1 normal <30 | A2 high 30–299 | A3 very high, nephrotic ≥300 |
| 1 | Kidney damage with normal or high GFR | ≥90 | | ✓ | ✓ |
| 2 | Kidney damage with mild reduction in GFR | 60–89 | | ✓ | ✓ |
| 3a | Mild-, moderate reduction in GFR | 45–59 | ✓ | ✓ | ✓ |
| 3b | Moderate-, severe reduction in GFR | 30–44 | ✓ | ✓ | ✓ |
| 4 | Severe reduction in GFR | 15–29 | ✓ | ✓ | ✓ |
| 5 | Kidney failure | <15 or dialysis | ✓ | ✓ | ✓ |

ACR, albumin to creatinine ratio.

**Table 2 Classification and stages of acute kidney injury**

| Criterion | Serum creatinine | Urine output |
|---|---|---|
| RIFLE classification | | |
| Risk | Serum creatinine increase to 1.5-fold or GFR decrease >25% from baseline | <0.5 mL/kg/h for 6 h |
| Injury | Serum creatinine increase to 2.0-fold or GFR decrease >50% from baseline | <0.5 mL/kg/h for 12 h |
| Failure | Serum creatinine increase to 3.0-fold or GFR decrease >75% from baseline or, serum creatinine ≥354 μmol/L (≥4 mg/dL) with an acute increase of at least 44 μmol/L (0.5 mg/dL) | <0.3 mL/kg/h × 24 h or anuria for 12 h |
| Loss | Total loss of kidney function >4 weeks | |
| End-stage kidney disease | End-stage kidney disease >3 months | |
| AKIN stages[3,4] | | |
| 1 | Serum creatinine increase ≥26 μmol/L (≥0.3 mg/dL) or increase to 1.5–2.0-fold from baseline | <0.5 mL/kg/h for 6 h |
| 2 | Serum creatinine increase >2.0–3.0-fold from baseline | <0.5 mL/kg/h for 12 h |
| 3 | Serum creatinine increase >3.0-fold from baseline or, serum creatinine ≥354 μmol/L (≥4.0 mg/dL) with an acute increase of at least 44 μmol/L (0.5 mg/dL) or, need for renal replacement therapy | <0.3 mL/kg/h for 24 h or, anuria for 12 h or, need for renal replacement therapy |

and blood urea nitrogen (BUN), has been confirmed by further studies.[9–13]

## Serum creatinine changes

An increase in serum creatinine may be present in 20–40% of patients hospitalized for HF.[9,14–17] This increase, generally defined as worsening renal function (WRF), has been associated with male gender,[17] elderly age,[18] a history of HF,[19,20] CKD,[16,17] diabetes,[17,21] anaemia,[22] hypertension,[19,20] a larger drop in blood pressure,[18,23,24] and high doses of diuretics.[16,19]

Higher creatinine levels and a larger increase in serum creatinine have been associated with a longer hospital stay, increased in-hospital and long-term mortality, and higher rehospitalization rates.[9,16,17,20,25–27] However, some studies did not find an independent association between an increase in serum creatinine and outcomes.[7,9,15,16,28,29]

Thus, differently from the absolute values, changes in serum creatinine may have a prognostic role in some, but not in all, of the patients. For example, increases in serum creatinine when angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are started are associated with long-term renal-protective effects and improved outcomes.[23,30] Changes after diuretic therapy in patients hospitalized for HF also seem unrelated to the prognosis.[28,29,31–33] These limitations of serum creatinine as a prognostic indicator have been shown only recently with studies in which serum creatinine levels were prospectively measured in unselected patients hospitalized for HF and/or used as an endpoint in randomized intervention trials.[17,18,21,22,24,25,28,31–33]

They are the basis for the search for new markers of kidney dysfunction (see below the specific section).

# Mechanisms leading to renal dysfunction in patients with heart failure

Heart failure may cause kidney dysfunction through multiple mechanisms (*Figure 1* and *Table 3*). They may interact with each other and their relative importance varies in each patient.

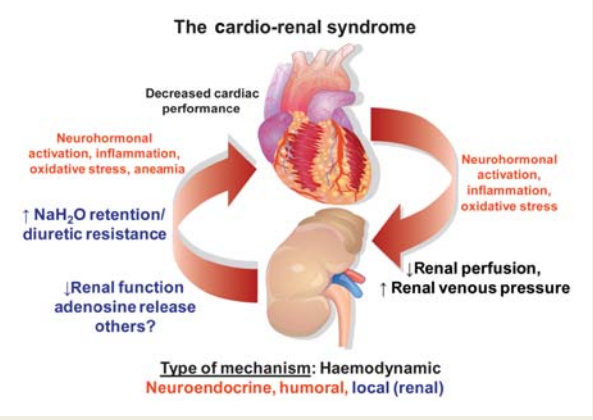


**Figure 1** Cardio-renal interactions in heart failure and kidney disease. Most of the mechanisms may be activated by each of the two conditions and are able to affect both cardiac and renal function. These mechanisms can be subdivided into haemodynamic, neuro-hormonal and inflammatory, and local.

**Table 3 Mechanisms involved in the cardio-renal interactions**

| Mechanisms | Causing renal injury in HF | Causing cardiac damage in CKD |
|---|---|---|
| Haemodynamic abnormalities: low renal blood flow and increased renal venous pressure | +++ | + |
| Neurohormonal activation: SNS and RAA | +++ | +++ |
| Inflammatory activation and oxidative stress | +++ | +++ |
| Abnormalities of the coagulation/ fibrinolytic system | 0 | +++ |
| Vascular calcification | 0 | +++ |
| Anaemia | + | +++ |
| Diuretic treatment of HF | +++/+ | 0 |

RAA, renin–angiotensin–aldosterone; SNS, sympathetic nervous system.
+ indicates slightly related; ++ and +++ indicate the presence and the extent of the effect; 0 indicates no clear relationship.

Importantly, as outlined in the previous section and shown in *Figure 2*, short-term changes in serum creatinine levels do not necessarily evolve into long-term changes and nephron loss.

## Haemodynamic abnormalities

The kidney is sensitive to haemodynamic changes, such as an increased central venous pressure ('renal afterload') and a reduced cardiac output ('renal preload'). In patients with decompensated HF, increased central venous pressure and/or intra-abdominal pressure are strong determinants of increased serum creatinine levels.[34–39] Reduced cardiac output is another major determinant of renal impairment in HF (*Figure 3*).[36,40,41]

## Sympathetic hyperactivity

The kidneys are richly innervated by efferent sympathetic nerve fibres and the renal sympathetic drive is markedly increased in HF. Even mild and low-frequency stimulation of efferent sympathetic nerves enhances sodium reabsorption. Increased stimulation decreases the renal blood flow, through renal artery constriction, and stimulates renin release by the juxtaglomerular cells.[42]

## Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS) is activated in HF. Initially, angiotensin II may cause preferential vasoconstriction of the glomerular efferent arteriole, favouring glomerular filtration, despite low renal blood flow.[30,40,43] In the long term, RAAS activation has untoward effects on the kidney including the stimulation of inflammatory pathways, fibrosis, increased oxidative stress, and endothelial dysfunction. These mechanisms are the basis for the long-term protective effects of ACE inhibitors and ARBs.[30]

## Adenosine release

Adenosine release may contribute to renal dysfunction, e.g. after high-dose furosemide. However, rolofylline, a type 1A adenosine antagonist, had no effects on long-term outcomes.[44]

## Inflammation and oxidative stress

Inflammation may play a pivotal role in cardio-renal interactions. Volume overload and venous congestion cause inflammatory activation in HF.[45]

## Anaemia

Anaemia is associated with poor outcomes both in HF and CKD. Renal dysfunction causes a depression of erythropoietin production. The inflammatory activation associated with HF inhibits renal erythropoietin production, causing resistance to erythropoietin and iron deficiency, through reduced absorption and decreased release from stores in macrophages and hepatocytes.[46]

## Effects of heart failure treatment on renal function

Many drugs used for the treatment of HF may influence renal function. Short-term changes in serum creatinine must be distinguished from long-term changes, which may be associated with nephron loss and permanent renal impairment (*Figures 3* and *4*). The

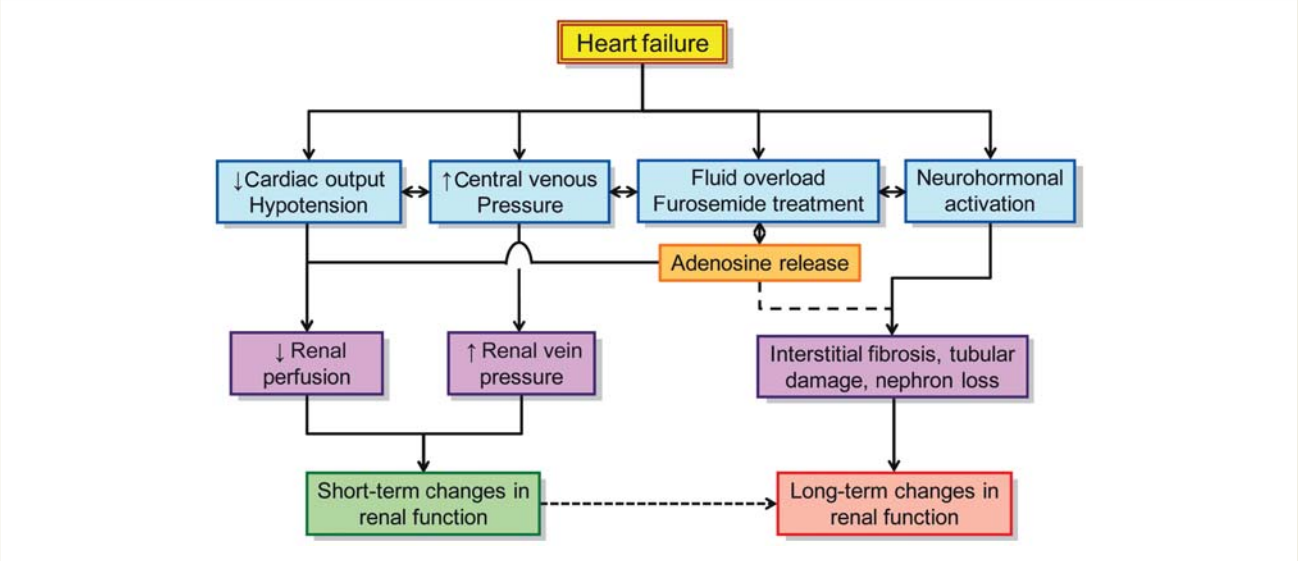


**Figure 2** Mechanisms of the impairment of renal function in heart failure.

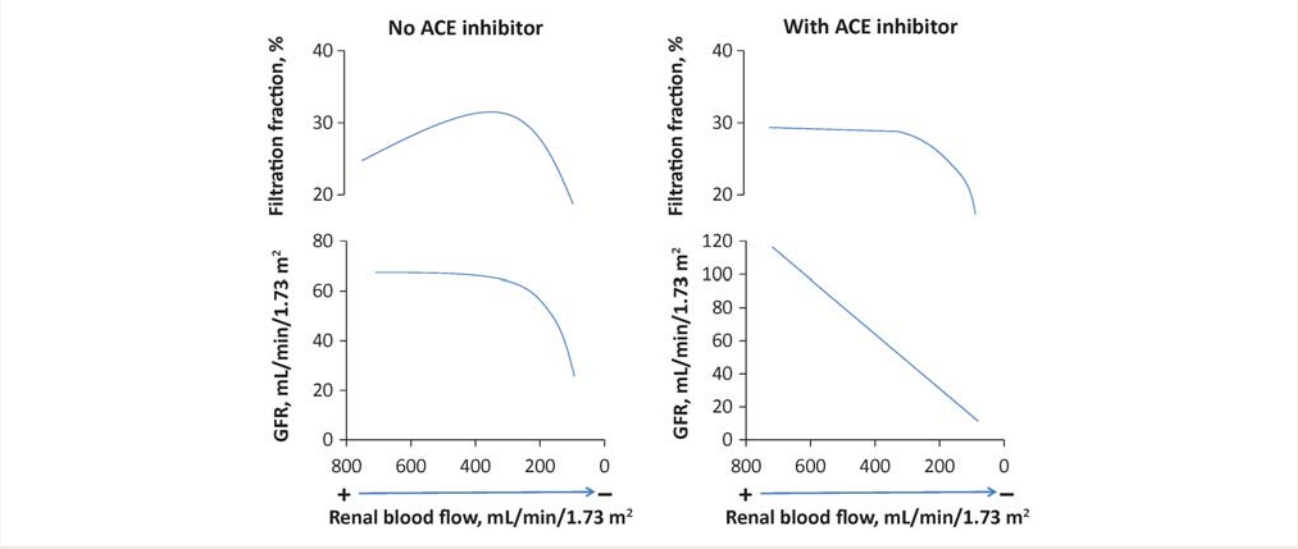


**Figure 3** Changes in the GFR when the cardiac output and the renal blood flow are reduced. In the absence of a blockade of the renin–angiotensin II system, preferential constriction of the efferent glomerular arteriole by angiotensin II increases the hydrostatic pressure in the glomerular capillaries allowing the maintenance of a constant GFR through an increase in the filtration fraction. This effect is blocked by renin–angiotensin inhibitors which, thus, make the kidney critically dependent only on renal blood flow. Modified from references.[40,41]

effects of the major drugs treating HF patients are outlined in *Table 4*.[30,47–51]

## Markers of renal dysfunction

Traditional markers of renal function have shown major shortcomings. This has prompted the research on new biomarkers, possibly able to detect AKI at earlier stages and more related with outcomes.

### Serum creatinine

Iothalamate or inulin clearances are the gold standards for measuring the GFR. However, these are time consuming and cannot be used routinely. Measurements based on serum creatinine have become routine clinical practice. Their value has been further enhanced by studies showing their prognostic value.[9,10,14,26,27] However, there are important limitations to the use of serum creatinine as a marker of renal function (*Table 5*).

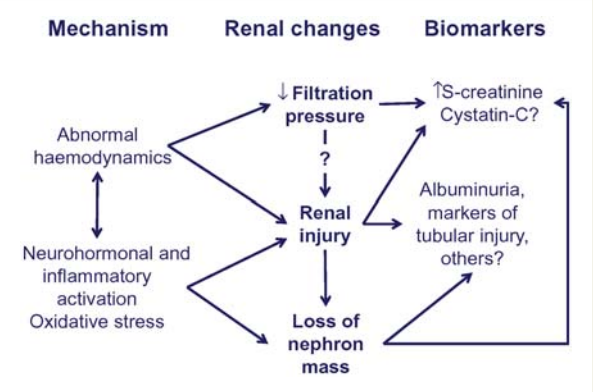


**Figure 4** Different biomarkers for different changes in renal function.

## Blood urea nitrogen

Blood urea nitrogen is an important predictor of morbidity and mortality in HF. Multiple studies have shown that it has a greater prognostic value than serum creatinine.[9–12,33,52] Paradoxically, the prognostic value of BUN may be caused by its relation to other variables, such as neurohormonal activation, protein intake, nitrogen production, and protein catabolism.[52,53]

Thus, better and earlier markers of renal dysfunction are needed. Some of them are summarized below and in *Table 6*.

## Cystatin-C

Cystatin-C is freely filtered by the glomerulus and then reabsorbed by the tubular epithelial cells where it is catabolized. Unlike creatinine, it is independent of the body mass, protein intake, or catabolism. Multiple studies have shown its greater accuracy as an index of the GFR. Its main advantage seems to be its greater sensitivity for the early detection of kidney dysfunction.[52,54–56]

## Albuminuria

Albuminuria, assessed as the albumin-to-creatinine ratio in urine, is an established criterion for the diagnosis of CKD.[1,2] Micro- and macro-albuminuria have been shown in ~20–30 and 5–10%, respectively, of the patients with HF.[57–60] The causes are, at least partially, independent of a reduced GFR and include concomitant diabetes and/or hypertension, haemodynamic abnormalities, increased intraglomerular pressure, and endothelial damage and tubular dysfunction with reduced reabsorption. Albuminuria has been associated with an increased risk of death that remains significant after adjustment for renal function or diabetes.[58–60]

## Tubular function markers

Tubular cells may be injured at an earlier stage than the glomerulus and therefore markers of tubular damage are potentially useful for the early detection of AKI (*Figure 4*).

## Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is produced by the kidney following ischaemic or toxic injury and is detectable in plasma and urine after AKI. Many studies have identified NGAL as an early marker of AKI.

Elevated serum NGAL levels, measured at the time of hospital admission, can predict the development of WRF and are a prognostic marker in patients with HF.[50,61,62] An increase in urinary NGAL has also been shown in patients with chronic HF and has been associated with an increased mortality risk independent of the GFR.[63–65]

## Kidney injury molecule 1

Kidney injury molecule-1 (KIM-1) is a marker for proximal tubular injury and is expressed in proximal tubular cells after AKI. It mediates the conversion of cells into phagocytes, which play a role in the immune response to injury. To date, it can only be measured in urine. In AKI, urinary KIM-1 has a strong predictive value for subsequent renal failure.[66]

## N-acetyl-beta-D-glucosaminidase

N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal brush border enzyme of the proximal tubule cells, released into the urine after tubular injury.[52] Both urinary KIM-1 and NAG are consistently increased in patients with HF in the presence of tubular damage and are associated with an increased risk of HF hospitalization or death, independent of the GFR.[63,64,67]

## Interleukin-18

Interleukin-18 (IL-18) is a cytokine quickly up-regulated in response to AKI. In a comparative analysis, IL-18 levels preceded the rise in serum creatinine, but its rise was slower compared with that of NGAL. It also has a low specificity, as, similar to other cytokines it also increases in other inflammatory conditions, such as arthritis and sepsis. To date, no studies have investigated its ability to predict AKI in patients with HF.[52]

# Conclusion and future perspectives

Interactions between the heart and kidney are complex and still incompletely understood. The progressive deterioration in renal function in HF patients is a result of multiple mechanisms including increased renal venous and intra-abdominal pressure, renal hypoperfusion, neurohormonal and inflammatory activation, adenosine release, and drug therapy for HF. Impaired renal function is, therefore, more likely a marker of greater HF severity than a mechanism contributing to HF progression.

The complete role of kidney dysfunction in the progression of HF is still unresolved. The prognosis seems mainly related to long-term changes in kidney function, rather than to short-term changes in serum creatinine. The importance of kidney dysfunction is also dependent on the underlying diseases (HF, but also, concomitant

**Table 4 Effects of pharmacological agents on renal function parameters**

| Drug | Mechanism(s) favouring WRF | Short-term effects | Long-term effects | Contraindications and dose changes based on renal function[47,48] | Procedures related to increased s-creatinine[47,48] |
|---|---|---|---|---|---|
| ACE-I/ARBs | Dilation of the efferent glomerular arteriole: reduced filtration pressure | ↑ S-creatinine | Beneficial effects on multiple mechanisms of CKD (interstitial fibrosis, oxidative stress, inflammation) | Contraindicated with bilateral renal artery stenosis or s-creatinine >220 μmol/L (2.5 mg/dL) | ↑S-creatinine <50% from baseline or to 265 μmol/L (3 mg/dL), is acceptable; half the dose with s-creatinine, 265–310 μmol/L (3–3.5 mg/dL); stop with s- creatinine >310 μmol/L (3.5 mg/dL) |
| Beta-blockers | Indirect, through changes in cardiac function | None | None | | |
| Aldosterone antagonists | Arterial underfilling (?) | Slight ↑ s-creatinine[49] | Beneficial effects on multiple mechanisms of CKD (interstitial fibrosis, oxidative stress, inflammation) | Contraindicated with s-creatinine >220 μmol/L (2.5 mg/dL); Use with caution in CKD because of hyperkalaemia risk | Half the dose if serum creatinine rises to >220 μmol/L (2.5 mg/dL); stop if creatinine >310 μmol/L (3.5 mg/dL) |
| Diuretics | Arterial underfilling; tubuloglomerular feedback; neurohormonal activation | ↑S-creatinine[16,19,20,29,31] | Potentially deleterious because of neurohormonal activation | Avoid thiazides when GFR <30 mL/min; need higher doses for loop diuretics | Check for dehydration; avoid other agents associated with WRF; consider ultrafiltration |
| Vasopressin antagonists | Arterial underfilling (??) | No change | Potentially beneficial | None | None |
| Digoxin | None | None | | Use lower doses | |
| Vasodilators (e.g. nitrates) | Drop in blood pressure, hypotension | ↑ S-creatinine if hypotension | Unknown | Consider lower doses in severe CKD | Avoid hypotension |
| I.V. inotropic agents | ↑ cardiac output and renal perfusion | ↓ creatinine (?), ↓ need of diuretics | Unknown | | |
| Nesiritide | Hypotension | ↑ S-creatinine if hypotension | No change[51] | Caution in hypotension | Avoid hypotension |
| Dopamine | Renal vasodilation through dopamine type 1 receptors | ↓ S-creatinine (?) | No change | | |
| Aspirin, NSAIDs | Inhibition of prostacyclin synthesis; constriction of the afferent glomerular arteriole, reduced filtration pressure | ↑ S-creatinine | Unknown | | Withdraw in case of ↑ s-creatinine |

S, serum; NSAIDs, non-steroidal anti-inflammatory drugs.

diabetes, hypertension, or intrinsic glomerular disease) and these need to be evaluated in each patient. New markers of glomerular and tubular function are providing additional prognostic information, and might allow an earlier detection of kidney injury. However, their relative role in clinical practice has not been completely established, yet.

Thus, the evaluation of renal function in patients with HF is important as it may reflect their haemodynamic status and provide a

**Table 5 Limitations of serum creatinine as a marker of renal dysfunction**

| |
|---|
| Variable relationship with GFR |
| Creatinine generation is dependent on dietary intake and muscle mass |
| Creatinine is secreted by proximal tubular cells |
| Inter-individual variability |
| Influenced by concomitant drugs (trimethoprim, cimetidine, and dronedarone) |
| Extrarenal degradation by intestinal bacteria |
| Exponential relation of serum creatinine changes with renal function |
| Not sensitive to renal injury in the early stages of renal damage |
| Overestimates renal damage in advanced renal dysfunction |
| Not sensitive to tubular damage |
| Slow kinetics with late detection of kidney injury |
| Sensitive to changes in volume status and renal haemodynamics unrelated to renal damage (i.e. diuretic treatment, initiation of ACE inhibitors or ARBs)[30,31,33,40,43] |

**Table 6 Biomarkers of renal injury and function**

| Biomarker | Advantages | Pitfalls |
|---|---|---|
| Serum creatinine | Universally present<br>Used for GFR estimation | see *Table 5* |
| Blood urea nitrogen | Universally present | Also an index of neurohormonal activation and nutritional state |
| Serum cystatin-C | High, independent, prognostic value<br>Accurate measurement of GFR | Slightly influenced by thyroid function, malignancy, corticosteroid therapy |
| | Early increase after AKI, compared with creatinine<br>High prognostic value | Not widely available |
| Serum β-trace protein | Accurate measurement of GFR | Also increased in hypertension, inflammation, endothelial dysfunction, and atherosclerosis |
| | High prognostic value for death and HF rehospitalizations | Not widely available |
| Albuminuria | Widely available<br>Prognostic value | May be caused by diabetes and/or hypertension, increased intraglomerular pressure |
| Serum or urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) | Marker of tubular damage<br>Prognostic value | Better prognostic value with urinary measurements, to date<br>May be influenced by inflammation, sepsis or cancer |
| Urinary kidney injury molecule 1 (KIM-1) | Marker of tubular damage<br>High prognostic value | Only measurable in urine |
| N-acetyl-beta-D-glucosaminidase (NAG) | Marker of tubular damage<br>High prognostic value, above all when combined with NGAL and KIM-1 | Only measurable in urine |
| Serum interleukin-18 (IL-18) | Early rise after AKI | Low specificity: increases with inflammatory conditions (sepsis, arthritis) |
| Fatty acid-binding protein (FABP) | Early response following ischaemic injury | Low specificity<br>No data in HF |

better prognostic assessment. The prevention of renal dysfunction with new therapies might also improve outcomes although strong evidence is still lacking.

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