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REVIEW

Renal impairment and worsening of renal function in acute heart failure: can new therapies help? The potential role of serelaxin

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Abstract Renal dysfunction is a frequent finding in patients with acute heart failure (AHF) and an important prognostic factor for adverse outcomes. Worsening of renal function occurs in 30–50 % of patients hospitalised for AHF, and is associated with increased mortality, prolonged hospital stay and increased risk of readmission. Likely mechanisms involved in the decrease in renal function include impaired haemodynamics and activation of neurohormonal factors, such as the renin–angiotensin–aldosterone system, the sympathetic nervous system and the arginine–vasopressin system. Additionally, many drugs currently used to treat AHF have a detrimental effect on renal function. Therefore, pharmacotherapy for AHF should carefully take into account any potential complications related to renal function. Serelaxin, currently in clinical development for the treatment of AHF is a recombinant form of human relaxin-2, identical in structure to the naturally occurring human relaxin-2 peptide hormone that mediates cardiac and renal adaptations during pregnancy. Data from both pre-clinical and clinical studies indicate a potentially beneficial effect of serelaxin on kidney function. In this review, we discuss the mechanisms and impact of impairment of renal function in AHF, and the potential benefits of new therapies, such as serelaxin, in this context.

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Introduction

Patients with acute heart failure (AHF) frequently present with or have a history of renal impairment [1, 2] with a significant impact on outcomes. In a systematic review of 16 studies including 80,098 patients with heart failure (HF), 29 % of patients had moderate to severe renal impairment [3]. This is especially important as renal impairment, assessed using glomerular filtration rate (GFR), is a strong predictor of mortality in patients with both ischaemic and non-ischaemic HF (Fig. 1) [4, 5]. In contrast, lower left ventricular ejection fraction (LVEF) and greater clinical severity of the disease only moderately increase mortality risk [4].

Renal impairment is also associated with an impact on other outcome measures. A retrospective analysis of 33,901 patients with AHF from a large managed care database from the United States of America showed that moderately reduced renal function (GFR <60 ml/min; Stages 3–5, as defined by the Chronic Kidney Disease (CKD)-Epidemiology Collaboration Group) was associated with a higher rate of all-cause readmissions (47 vs. 39 %), HF-related readmissions (31 vs. 21 %) and mortality at 6 months (14 vs. 9 %) when compared with patients with normal/mild reduction in GFR (≥60 ml/min; Stages 1–2) [6].

Moreover, worsening renal function (WRF) has been observed in 20–30 % of patients during hospitalisation for AHF [7, 8], and another 12 % of patients develop WRF following discharge [9, 10]. WRF is typically defined as an increase in serum creatinine of ≥0.3 mg/dl from the baseline value [11], although other measures such as reduced estimated GFR

(≥25 %) and increased levels of plasma cystatin C (≥0.3 mg/l) and blood urea nitrogen (≥25 %) may also be indicative of WRF [12, 13]. Most recently, a precise terminology and definition of changes in renal function in AHF have been proposed, adapting the criteria of acute kidney injury (AKI) (Table 1) [14]. AKI and WRF are often recognised as distinct entities; AKI is indicative of renal injury, while WRF results from a functional decline in GFR, which may occur in the absence of AKI [14]. Monitoring clinical response(s) and measures of renal function may aid identification of true AKI in patients with AHF [14]. WRF probably reflects organ damage occurring during the acute phase and, in turn, impacts prognosis. For example, studies suggest that WRF is associated with increased duration of hospitalisation and readmission rates and might also be accompanied by increased mortality [3, 15–17]. Indeed, the recent RELAX-AHF study showed that WRF, defined by an increase in cystatin C of ≥0.3 mg/l at Day 2, was associated with increased 180-day mortality (Fig. 2) [18]. It is notable that many current treatments for AHF do not protect the kidney and some, such as diuretics, may even contribute to WRF [13, 19–21]. Clinically, the occurrence of WRF should not be considered in isolation and needs to be taken in the context of the broader profile of the presenting patient—Metra et al. [22] demonstrated that WRF has prognostic utility only in patients who also showed persistent signs of congestion, and not in those without congestion. Furthermore, in a separate analysis of the RELAX-AHF study data, greater incidences of the composite of cardiovascular mortality and/or rehospitalisation for HF or renal failure at Day 60, and cardiovascular mortality alone at Day 180, were observed in patients with both WRF (defined as an increase in serum creatinine of ≥0.3 mg/dl at Day 4/5) and poor diuretic response (lower than the median response; defined as weight loss per unit of diuretic dose) at Day 5, compared with patients with WRF and good diuretic response, as well as patients without WRF with both good and poor diuretic responses (interactions not significant) [23]. This suggests that a good diuretic response may be indicative of a lower risk of cardiovascular mortality and hospitalisation for HF or renal failure in patients with WRF.

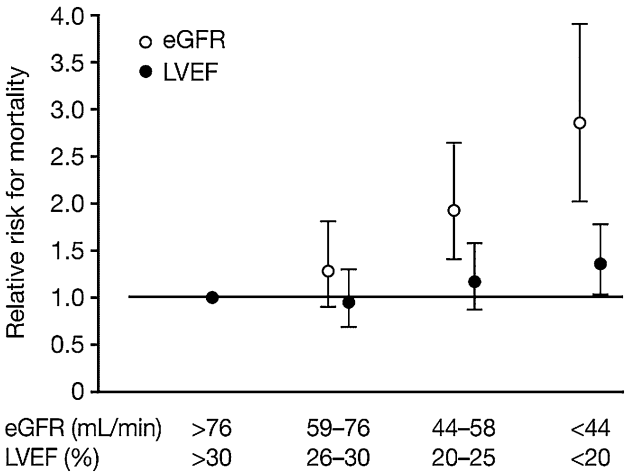

Fig. 1 Relationship between left ventricular ejection fraction (LVEF), glomerular filtration rate (GFR) and mortality. Reproduced with permission of Wolters Kluwer Health: Hillege et al. [4]. Data presented as quartiles and assessed using a multivariate proportional hazards regression model. *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction

In this review, we consider the mechanisms and impact of renal impairment and WRF in AHF, and the potential benefits of new therapies, such as serelaxin, in this context.

Mechanisms underlying the development of renal impairment and worsening of renal function in AHF

Renal and cardiac dysfunction are closely related, forming the basis of the concept of the cardiorenal syndrome, which has been described in detail elsewhere [24]. The complex cross-talk between the two organs is important for the

Table 1 Characteristics of the definition of AKI in patients with AHF

Suggested definition of AKI in AHF[a]	
Serum creatinine/urine output	Additional criteria
Increase 1.5–1.9 times baseline sCr within 1–7 days before or during hospitalisation	Deterioration in HF status or failure to improve OR need for inotropes, ultrafiltration or renal replacement therapy
OR ≥26.5 μmol/l increase in sCr[b] within 48 h	
OR urine output <0.5 ml/kg/h for 6–12 h	

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AHF acute heart failure, *AKI* acute kidney injury, *h* hour, *HF* heart failure, *RAAS* renin–angiotensin–aldosterone system, *sCr* serum creatinine

[a] Any deterioration in renal function that does not meet these criteria should be regarded as pseudo-AKI where there is no evidence of associated harm with the exception of very large increases in serum creatinine (doubling or >88.4 μmol/l increase) which should always be a reason to refer for further investigation. Consider alternative reasons for increases in creatinine/cystatin C other than AKI such as intravascular depletion, dehydration, excessive diuresis, medication that alters tubular handling of creatinine, and RAAS inhibitors

[b] Or ≥0.3 mg/l increase in cystatin C

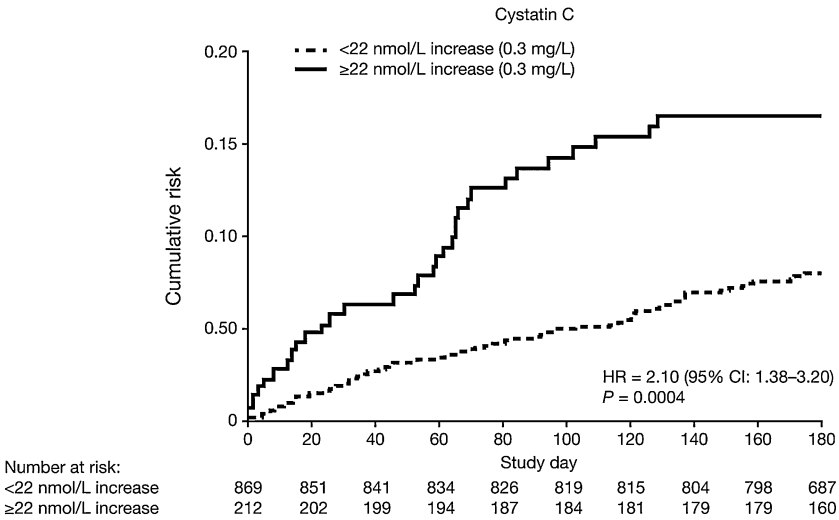

Fig. 2 Cumulative risk of all-cause death through Day 180 in the RELAX-AHF study. Patients subdivided by acute changes in renal function (cystatin C) from baseline to Day 2. Reproduced with permission of Elsevier open access licence: Metra et al. [18]

control of blood pressure, sodium and water excretion, arterial perfusion, tissue oxygenation and extracellular fluid balance [24, 25]. Thus, dysfunction of one organ may adversely affect the function of the other organ.

Renal impairment in patients presenting with AHF

It is likely that much of the renal impairment observed in patients presenting with AHF, including de novo AHF and decompensation in patients with chronic HF (CHF), is caused by comorbidities or risk factors, such as hypertension, diabetes mellitus, obesity, smoking or renal atherosclerosis [26, 27]. Kidney damage through the activation of inflammatory cytokines has been observed in patients with atherosclerotic disease [26]. Hypertension and diabetes are associated primarily with glomerular damage, which may be caused by impaired renal autoregulation increasing renal sensitivity to fluctuations in blood pressure and leading to impaired GFR. Disease progression is associated with the occurrence of glomerulosclerosis, interstitial fibrosis and the loss of nephrons. These conditions lead to water and sodium retention resulting in the upregulation of compensatory pathways, such as the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system and activation of the calcium-parathyroid axis [28, 29]. Additionally, the loss of nephrons contributes to exacerbation of existing hypertension and to pressure and volume overload [29]. A consequence of the upregulation of compensatory pathways is the release of profibrotic factors, such as galectin-3 and tumour growth factor-β (TGF-β), which may contribute to the development of additional cardiovascular complications [29].

During an AHF event, systemic vasoconstriction and decreased cardiac function can lead to increased cardiac pre- and afterload and increased left ventricular filling pressures [10, 30]. This, in turn, leads to congestion and hypoperfusion, with neurohormonal activation, inflammation, oxidative stress and haemodynamic abnormalities, leading to organ dysfunction, including renal dysfunction [31–33]. Impaired renal function contributes to water and sodium retention and further impacts on cardiac function as described above [10].

Renal impairment and WRF during AHF can therefore be considered to be part of a multifactorial process which involves several mechanisms (Fig. 3) [34]. The worsening may result from haemodynamic or neurohormonal disturbances occurring during the AHF episode [10, 24].

Haemodynamic disturbances

Several regulatory mechanisms control renal blood flow and the glomerular filtration pressure through vasoconstriction and vasodilation of the afferent and/or efferent arterioles, allowing the kidney to maintain GFR and renal blood flow under various physiological conditions. However, the kidney is susceptible to haemodynamic changes, such as reduced cardiac output, frequent drops in systolic blood pressure and elevated central venous pressure, all of which are observed in AHF [33–36]. Reduced cardiac output results in systemic and renal hypoperfusion, leading to the release of renin by juxtaglomerular cells in the afferent arterioles [15]. As a consequence, the RAAS is activated and the sympathetic nervous system is stimulated by angiotensin II. This leads to sodium and water retention, volume expansion, increased systemic vascular resistance and ventricular remodelling [37]. Additionally, an increase in central venous pressure (backward HF) leads to an elevated glomerular efferent arteriole pressure, and is accompanied by a reduction in the glomerular filtration pressure gradient, fall in GFR, and also sodium and water retention [11, 38–40]. Reduced renal function also impacts the clearance of metabolic waste products such as uric acid,

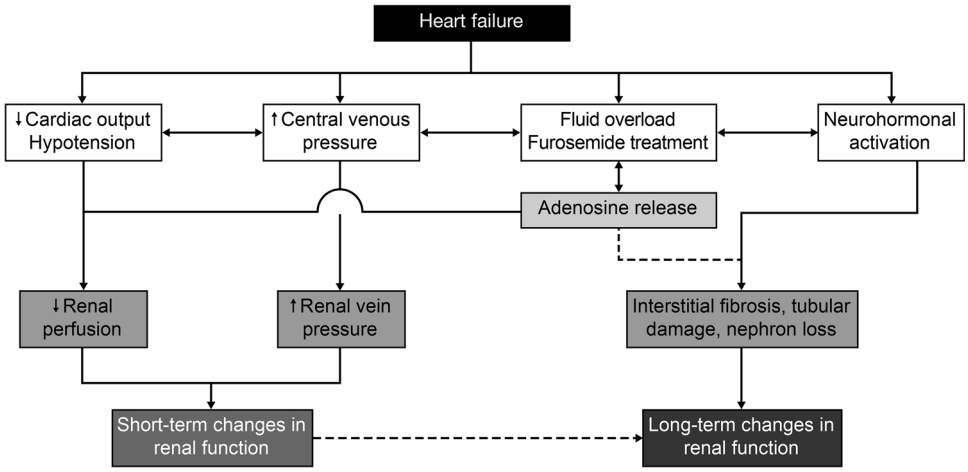

Fig. 3 Mechanisms involved in the impairment of renal function associated with heart failure. Reproduced by permission of Oxford University Press and the American College of Cardiology Foundation: Metra et al. [34]

a by-product of purine metabolism [41]. Uric acid serves as a good indicator of oxidative stress and tissue damage. Elevated levels may indirectly cause endothelial dysfunction and impair regulation of vascular tone. Additionally, increased levels of uric acid are associated with inflammation, morphological and functional changes in the glomeruli and renal arteriole and increased salt-sensitivity—hyperuricemic or salt-sensitive kidney-dependent hypertension.

Neurohormonal activation

Initially in patients with HF, over-activity of the sympathetic nervous system with elevated levels of circulating catecholamines (in particular, epinephrine and norepinephrine) and RAAS hormones (angiotensin II and aldosterone), represents a useful compensatory mechanism for maintaining homoeostasis of the circulatory flow in the context of declining cardiac function [11, 34, 42, 43]. However, with progression of HF, maladaptive changes occur with excessive increase of these hormones, which leads to vasoconstriction and volume dysregulation. This, in turn, results in an increase of peripheral vascular resistance and a further deterioration of LV function, initiating a vicious cycle. Although vasoconstriction is accompanied by a simultaneous increase in vasodilating hormones, such as natriuretic peptides, prostacyclin and nitric oxide, the effect is not strong enough to offset the overall detrimental increase in peripheral vascular resistance [11, 34, 44].

The effect of current pharmacological therapy for AHF on renal function

Current treatment guidelines for AHF recommend the use of diuretics, vasodilators and natriuretic peptides as well as other pharmacological agents [45, 46]. However, many of these agents have a profound impact on renal function (Table 2) [34, 45, 46]. For example, loop diuretics have been implicated in WRF, via mechanisms of arterial underfilling, activated tubuloglomerular feedback with vasoconstriction of the vas afferens and neurohormonal activation [34, 46]. They may impair the kidneys' ability to excrete and dilute urine. They are further associated with an immediate decrease of GFR and an increase in serum creatinine [22, 34]. Vasopressin-2 receptor antagonists have potentially beneficial long-term effects; however, they may impair renal function by arterial underfilling [34]. Vasodilators, such as nitrates, and natriuretic peptides, such as nesiritide, cause a drop in blood pressure and hypotension; treatment with vasodilators can also lead to an increase in serum creatinine [34, 47]. Nesiritide may provide early relief of dyspnoea in patients with AHF, and while early analyses indicated possible concerns regarding renal impairment, analysis of the ASCEND-HF study reported no increase in the incidence of WRF (defined as an increase of serum creatinine of >0.3 mg/dl and a change of ≥25 %) with nesiritide vs. placebo [48, 49]. Not all agents for the treatment of AHF have been reported to worsen renal function. Intravenous inotropic agents that increase cardiac output and renal perfusion may decrease creatinine levels and reduce the need for diuretics [34, 45]; however, the use of inotropic agents is limited due to possible induction of myocardial ischaemia and arrhythmia, and concerns regarding increased mortality [45, 50, 51]. In addition, treatment with levosimendan, an inodilator, has been shown to improve renal blood flow and/or GFR in patients with AHF, when compared with placebo [52] and dobutamine [53]. Reduced serum creatinine levels have also been reported following levosimendan treatment [52].

Interestingly, non-pharmacological treatment of AHF may also influence renal function. Ultrafiltration, which is

Table 2 Effect of therapeutic agents on renal function over the short and long term

Drug	Mechanism(s) favouring WRF	Short-term effects	Long-term effects
Diuretics	Arterial underfilling; tubuloglomerular feedback; neurohormonal activation	↑ S-creatinine ↑ Uric acid ↓ S-potassium	Potentially deleterious because of neurohormonal activation
Vasopressin antagonists	Arterial underfilling (??)	No change	Potentially beneficial
Vasodilators (e.g. nitrates)	Drop in blood pressure, hypotension	↑ S-creatinine if hypotension	Unknown
Intravenous inotropic agents	↑ cardiac output and renal perfusion	↓ Creatinine (?), ↓ need of diuretics	Unknown
Nesiritide	Hypotension	↑ S-creatinine if hypotension	No change
Dopamine	Renal vasodilation through dopamine type 1 receptors	↓ S-creatinine (?) ↑ Renal perfusion	No change

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recommended for the treatment of patients with AHF who are resistant to diuretic therapy [45, 46], was associated with increased creatinine levels in patients with AHF, persistent congestion and worsened renal function (defined as an increase in serum creatinine of ≥0.3 mg/dl), when compared with stepped pharmacological therapy, which included the use of diuretics, vasodilators and inotropic agents [54].

There has been some debate that short-term changes in renal function (particularly when assessed using serum creatinine levels) are less related to outcomes than deterioration of kidney function that occurs over longer time periods. In theory, the latter are more likely to be related to neurohormonal activation leading to nephron loss, renal fibrosis and permanent renal impairment [34]. However, a recent study in patients with AHF, included in the ADHERE registry and linked to Medicare claims in the USA, suggests that both transient and persistent WRF, assessed using serum creatinine and defined as any increase in serum creatinine ≥0.3 mg/dl from admission, are associated with significantly higher 90-day post-admission mortality compared with no WRF [55]. Furthermore, transient increases in serum creatinine have been shown to be related to longer cumulative length of hospital stay and higher costs than either no WRF or persistent WRF in 55,436 patients with AHF included in a large database [56]. These new findings suggest that the WRF events observed with some current therapies for AHF are clinically relevant.

Therefore, key treatment goals in patients with AHF are the amelioration of symptoms, the improvement of haemodynamics and the preservation of organ function in order to improve short- and long-term outcomes [34, 45]. Given that current treatment strategies for AHF may contribute to WRF, it is important that the therapeutic considerations also account for their potential impact on short- and long-term renal function.

Serelaxin: potential benefits on renal function

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone that mediates cardiac and renal adaptations during pregnancy [57]. Studies in both animals and humans have shown that serelaxin receptors are located in the heart tissue, blood vessels and the kidneys [57–60]. Binding of serelaxin to its G-protein-coupled receptors (known as relaxin family peptide or RFXP receptors) initiates multiple signalling pathways with systemic and renal haemodynamic effects [61]. Binding of serelaxin to the RFXP1 receptor on endothelial cells has been shown to mediate systemic arterial and renal vasorelaxation via the release of nitric oxide (NO) (the term vasorelaxation is used to differentiate serelaxin from classical vasodilators such as nitrates, which mediate systemic vasodilation, while the vascular effects of serelaxin appear to be specific to certain vascular beds [62]) [63]. In pre-clinical studies, serelaxin has been shown to have positive effects on pulmonary congestion and the symptoms of AHF. Furthermore, anti-inflammatory, anti-oxidant, anti-apoptotic cell death, anti-fibrotic and pro-angiogenic effects have been reported, all of which may contribute to organ protection [64–73].

These studies suggested that serelaxin has beneficial effects in the kidneys, protecting them from damage and remodelling. In an animal study in rats, serelaxin was found to increase both GFR and effective renal plasma flow [74]. Additionally, serelaxin treatment attenuated vasoconstriction initiated by medical angiotensin II [74]. Similarly, in another study in rats, serelaxin increased GFR as well as impacting renal circulation (by causing renal vasorelaxation and hyperfiltration) and osmoregulation (by reducing plasma osmolality and sodium concentration) [74]. A third study of long-term administration of serelaxin to rats demonstrated increases in GFR and effective renal plasma flow, with a decrease in effective renal vascular resistance [75]. Additionally, a significant decrease in glomerular and tubular collagen deposition was observed [75].

Subsequently, renal protective effects of serelaxin have been observed in humans. A study in healthy volunteers treated with serelaxin (0.2 μg/kg bolus followed by 0.5 μg/kg/h infusion for 4 h) demonstrated an increase of 47 % in renal blood flow when compared with baseline levels ($p < 0.0001$) within 30 min [76]. Furthermore, in a phase II study in patients with CHF, a 24-h infusion of serelaxin 30 μg/kg/day led to a significant increase in renal plasma flow (time-weighted average ratio to baseline in serelaxin-treated patients was 1.31 as compared with 1.13 in placebo-treated patients; $p = 0.004$) [77]. In both studies, the increase in renal plasma flow was not associated with a change in GFR. In addition, in the patients with CHF treated with serelaxin, there was a small reduction in the filtration fraction as compared with placebo (time-weighted average change from baseline, 1.20 in serelaxin-treated patients and 1.44 in placebo-treated patients; $p = 0.0004$), suggesting a reduction in intraglomerular pressure, which may preserve renal function [77]. Serelaxin may mediate these improvements in renal function via direct vasorelaxation of afferent and efferent renal vessels, through activation of the endothelial type B receptor and release of NO [63, 78]. Significant reductions in serum creatinine were observed in another open-label, single-centre, pilot study in patients with CHF treated with serelaxin (30 μg/kg/day for 8 h; $p < 0.05$ vs. baseline) [79]. This study also showed trends towards an increase in the cardiac index as well as a decrease in pulmonary wedge pressure and circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, the latter findings being consistent with decreased cardiac stress [79]. Consequently, the beneficial effects of serelaxin treatment on renal function may result, in part, from improved decongestion.

A recent double-blind, multicentre phase II study in 71 patients with AHF evaluated the haemodynamic effects of serelaxin treatment and assessed the impact on renal function in 34 patients as compared with placebo ($n = 37$) [80]. Treatment with serelaxin resulted in an 11 % increase in creatinine clearance as compared with a 21 % decrease in the placebo-treated group during the treatment period. Both groups of patients had similar creatinine clearance rates at baseline. Treatment with serelaxin resulted in an increase of 20 % from baseline in creatinine clearance values; in the placebo-treated group, creatinine clearance decreased by 24 % from baseline, indicating a significant treatment difference of 39 %. Urine flow rates decreased in both treatment groups as compared with baseline and were deemed related to the study design by the authors as patients received intravenous loop diuretic administration 4 h prior to treatment initiation and after 8 h of treatment.

The largest study to date, RELAXin in AHF (RELAX-AHF), was a phase III, multicentre, randomised, double-blind, placebo-controlled study designed to investigate the efficacy and safety of serelaxin in the treatment of AHF in patients with mild-to-moderate renal insufficiency [defined as estimated (e)GFR 30–75 ml/min/1.73 m^2] [81]. Patients included in the RELAX-AHF study were hospitalised for AHF with systolic blood pressure >125 mmHg, increased levels of NT-proBNP, and were randomised within 16 h of presentation to treatment with either serelaxin (30 μg/kg/day as a 48-h intravenous infusion) or placebo in addition to treatment with standard of care [81]. The study primary endpoints were assessment of dyspnoea improvement from baseline in the visual analogue scale area under the curve (VAS AUC) to Day 5 and the proportion of patients with moderate or marked dyspnoea improvement measured by the Likert scale. In the study, serelaxin treatment improved the VAS AUC primary dyspnoea endpoint as compared with placebo ($p = 0.007$), but had no effect on the second primary endpoint as assessed by the Likert scale ($p = 0.70$) [81]. Serelaxin was associated with significant reductions in early (in-hospital) worsening of heart failure ($p < 0.001$ as compared with placebo), signs and symptoms of congestion, initial length of hospital stay and duration of intensive care treatment [81]. In serelaxin-treated patients, cardiovascular and all-cause mortality at Day 180 were significantly reduced by 37 % at 6 months [81]. Additionally, serelaxin treatment was associated with a significant reduction in the use of loop diuretics and fewer patients treated with serelaxin had adverse events related to renal impairment as compared with placebo [81].

Interestingly, a reduced incidence of WRF (defined as increases in serum creatinine and plasma cystatin C at Day 2 of ≥0.3 mg/dl and ≥0.3 mg/l, respectively) as well as lower levels of biomarkers that are indicative of renal dysfunction, specifically tubular necrosis [creatinine and cystatin C (markers of GFR) and urea (general marker of renal function)] were observed in serelaxin-treated patients compared to placebo (Fig. 4) [18]. This effect on biomarkers of renal dysfunction may help to explain the underlying mechanisms for improved mortality in RELAX-AHF. The observed reduction in 180-day cardiovascular and all-cause mortality in the serelaxin group was more pronounced in the subgroup of patients with moderate renal impairment (GFR <60 ml/min/1.73 m^2) (Table 3) [81, 82]. Taken together, these data from pre-clinical and clinical serelaxin studies provide further support for the protective effects of serelaxin in the kidneys.

Serelaxin: ongoing studies and current status

Serelaxin was approved by the Ministry of Health in Russia in 2014; additional data were requested by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) following initial submissions for approval [83]. An additional Phase III trial, RELAX-AHF 2, began in

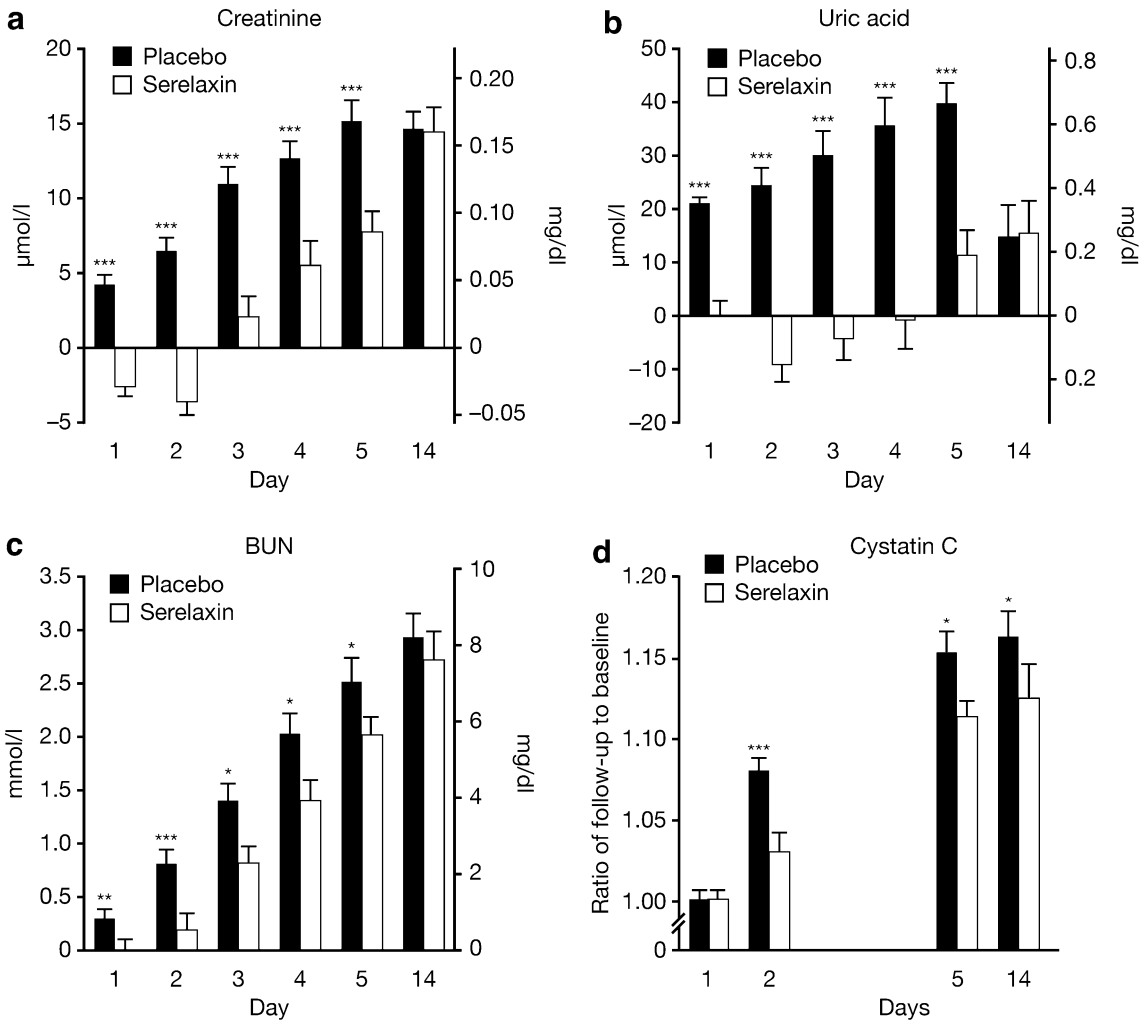

Fig. 4 Change from baseline in biomarkers of renal dysfunction in patients treated with serelaxin or placebo in the RELAX-AHF study. Reproduced with permission of Elsevier open access licence: Metra et al. [18]. **a–c** $*p < 0.05$, $**p < 0.005$, and $***p < 0.001$ by 2-sided, 2-sample t-test for serelaxin versus placebo. **d** $*p < 0.05$, $**p < 0.005$, and $***p < 0.001$ versus placebo by repeated measures analysis of variance with adjustment for baseline value. *BUN* blood urea nitrogen

Table 3 Post hoc analysis of the relationship between renal impairment at baseline and 180-day cardiovascular and all-cause mortality [81, 82]

	Baseline eGFR <60 [82]	Baseline eGFR <50 [82]	Total RELAX-AHF [81]
CV death, HR (95 % CI)	0.53 (0.33, 0.86); $p = 0.0103$	0.42 (0.23, 0.76); $p = 0.0040$	0.63 (0.41, 0.96); $p = 0.028$
AC death, HR (95 % CI)	0.53 (0.34, 0.83); $p = 0.0051$	0.44 (0.26, 0.74); $p = 0.0021$	0.63 (0.43, 0.93); $p = 0.020$
NNT	19	13	29

AC all-cause, *CV* cardiovascular, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *NNT* number needed to treat

September 2013 to further determine the effects of serelaxin on cardiovascular mortality in 6375 patients with AHF [84]. The results of the RELAX-AHF-2 trial are expected in 2016 [84]. Further studies in patients with AHF are ongoing, including the geographically specific RELAX-AHF-EU and RELAX-AHF-Asia studies [85, 86]. These studies include endpoints assessing effects on renal function that will further inform understanding of the effects of serelaxin [84–86].

Conclusions

Renal impairment and WRF during hospitalisation are common in patients presenting with AHF. Impairment of renal function is associated with adverse outcomes and should be considered as part of patient management. Current therapies for the treatment of AHF patients do not include renal protective measures. Rather, some drugs may

even contribute to WRF. Interestingly, serelaxin exhibits potentially beneficial effects on mortality and symptom amelioration and on renal function in patients with AHF. Thus, serelaxin has the potential not only to act as a potent treatment in AHF, but also to prevent WRF.

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Conflict of interest Roland E Schmieder: Received Speakers Bureau honoraria and is an advisory board member for Novartis. His University Hospital has also received grants from Novartis. Veselin Mitrovic: Employed by Kerckhoff-Klinik Forschungsgesellschaft mbH, has received grant/research support from Bayer and Novartis; honoraria from Bayer, Novartis and GlaxoSmithKline and is a consultant for Cardiorentis and a Board Member for Daichi Sankyo. Christian Hengstenberg: Received speakers bureau honoraria from AstraZeneca, Boehringer, Edwards, Novartis, and Symetis; Advisory Board member for Novartis.

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