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Role of comorbidities in heart failure prognosis Part 2: Chronic kidney disease, elevated serum uric acid

Andrea Tedeschi[1], Piergiuseppe Agostoni[2], Beatrice Pezzuto[2], Ugo Corra'[3], Domenico Scrutinio[4], Rocco La Gioia[4], Rosa Raimondo[4], Andrea Passantino[4] and Massimo F Piepoli[1]

Abstract

Despite improvements in pharmacotherapy, morbidity and mortality rates in community-based populations with chronic heart failure still remain high. The increase in medical complexity among patients with heart failure may be reflected by an increase in concomitant non-cardiovascular comorbidities, which are recognized as independent prognostic factors in this population. Heart failure and chronic kidney disease share many risk factors, and often coexist. The presence of kidney failure is associated with incremented risk of cardiovascular and non-cardiovascular mortality in heart failure patients. Chronic kidney disease is also linked with underutilization of evidence-based heart failure therapy that may reduce morbidity and mortality. More targeted therapies would be important to improve the prognosis of patients with these diseases. In recent years, serum uric acid as a determinant of cardiovascular risk has gained interest. Epidemiological, experimental and clinical data show that patients with hyperuricaemia are at increased risk of cardiac, renal and vascular damage and cardiovascular events. Moreover, elevated serum uric acid predicts worse outcome in both acute and chronic heart failure. While studies have raised the possibility of preventing heart failure through the use of uric acid lowering agents, the literature is still inconclusive on whether the reduction in uric acid will result in a measurable clinical benefit. Available evidences suggest that chronic kidney disease and elevated uric acid could worsen heart failure patients' prognosis. The aim of this review is to analyse a possible utilization of these comorbidities in risk stratification and as a therapeutic target to get a prognostic improvement in heart failure patients.

Keywords

Heart failure, comorbidities, kidney, uric acid, prognosis, risk stratification

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Heart failure: a syndrome of comorbidities

Over 80% of heart failure patients are ≥65 years of age and most of them suffer from one or more comorbidities, which crucially contribute to disease progression and may affect heart failure treatments.[1]

Non-cardiovascular comorbidities influence heart failure prognosis through shared risk factors or direct pathophysiological links.[2] The number of non-cardiac comorbidities predicts all-cause hospitalizations and even short-term mortality.[3]

The aim of this review is to analyse the physiopathological connections between elevated serum uric

[1]Cardiology Dept, Guglielmo da Saliceto Hospital, AUSL Piacenza and University of Parma, Italy
[2]Clinical Cardiology and Rehabilitation Unit, Università degli Studi di Milano, Centro Cardiologico Monzino IRCCS, Italy
[3]Cardiac Rehabilitation Division, IRCCS Istituti Clinici Scientifici Maugeri Spa SB, Italy
[4]Istituti Clinici Scientifici Maugeri-SPA SB. I.R.C.C.S. Institute of Bari, Italy

Corresponding author:
Andrea Tedeschi, Department of Cardiology, Parma University Hospital, Viale Antonio Gramsci, 14, 43126 Parma, Italy.
Email: andrea.tedeschimd@gmail.com

acid, chronic kidney disease (CKD) and heart failure, focusing on their prognostic impact.

CKD

CKD is a progressive condition defined by decreased kidney function, shown by reduced estimated glomerular filtration rate (eGFR) or markers of kidney damage, or both, for at least three months.[4]

Individuals with CKD have mortality rates that are more than double the rate in the general population and greater than 50% of deaths in patients with CKD are from cardiovascular disease (CVD):[5] in the presence of moderate or severe renal failure an individual is classified as being at high or very high risk of mortality, according the SCORE risk. In fact, CKD is a powerful independent risk factor for the development and progression of CVD and respective cardiovascular outcomes.[6–8] Development of heart failure is often observed in patients with CKD, and its prevalence increases significantly in cohorts with declining GFR.[9] Many of the same factors contribute to the development of both chronic diseases, including age, diabetes mellitus and hypertension.[10]

This brief review summarizes the data supporting the prognostic impact of CKD on heart failure patients; we will also describe the physio-pathological relationship between CKD and heart failure, and latest evidences on treatment strategies in patients affected by both conditions.

Prognostic significance of CKD in heart failure patients

CKD is present in 4.5% of the general population, while it has higher prevalence in heart failure, affecting up to 50% of patients with either a preserved or reduced ejection fraction.[11] Although patients with heart failure suffer poor outcomes, including a death rate of ≈50% within five years of diagnosis,[12] the co-occurrence of CKD and heart failure is associated with a doubling in the risk of all-cause mortality.[11]

Pathological consequences of CKD have been observed in a wide spectrum of heart failure patients. While Ahmed et al. reported that accompanying CKD was more strongly associated with mortality in patients with preserved ejection fraction (HFpEF) than in those with reduced ejection fraction (HFrEF),[13] a subsequent study demonstrated a similarly worse prognosis across the wide range of reduced eGFR levels in patients with either HFpEF or HFrEF.[14] Importantly, a reduced GFR is a stronger predictor of adverse outcome than a reduction in left ventricular ejection fraction in heart failure.[15]

Also, dynamic changes in renal function have been recognized to portend a poor prognosis.[16] However, every change should be interpreted considering the clinical context of the change in renal function. Increases in creatinine during an acute heart failure hospitalization are not always clinically relevant, especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration.[17] A similar line of reason can be applied to the worsening of renal function (WRF) occurring during initiation of neurohormonal antagonist therapy; in this setting, WRF could be a reflection of neurohormonal blockade and not necessarily a signal of direct renal injury.[18,19] Yet, mis-interpretation of these changes still results in inappropriate discontinuation of decongestive or neurohormonal blocker therapy in clinical practice.[20,21]

CKD and heart failure: bidirectional close link

In recent years, our understanding of the close interconnection between cardiac function and renal function has deeply evolved. Three key pathophysiological categories are currently thought to contribute to the development and progression of cardio–renal and reno–cardiac interactions:[22]

1. *Haemodynamic alterations* due to low cardiac output and/or altered venous return;
2. *Dysregulation* of the *neuro-hormonal axis* via sympathetic nerve activation and/or triggering of the renin–angiotensin–aldosterone system (RAAS);
3. *Other factors* that contribute to the accelerated progression of heart failure and CKD, including local and systemic inflammation, metabolic changes, anaemia, and bone and mineral disorder.

This important organ cross-talk has previously been extensively described.[23–25]

CKD and heart failure: a common therapeutic goal

Once diagnosed, appropriate heart failure treatment in CKD patients can be challenging. Most CKD–heart failure patients have HFpEF, where there are no current evidence-based recommendations for therapies that improve outcomes, although evidence-based HFrEF therapies, such as β-blockers and RAAS inhibitors, have been proved to be effective.[26,27]

Real-world observational data in ambulatory symptomatic HFrEF patients have shown a beneficial effect of angiotensin-converting enzyme (ACE)-inhibition also in patients with baseline CKD and in those who experienced a drop in eGFR after initiation of ACE inhibitor (ACE-I).[28] Fewer data are available for angiotensin receptor blockers (ARBs); however, a

propensity adjusted analysis illustrates a similar benefit on outcome despite presence of CKD.[29] It is still important to underline that there are no specific data from heart failure trials that treatment with ACE-I/ARB also reduces the slope of GFR decline. However ACE-I and ARB have shown to be reno-protective in patients with CKD and diabetes, who still constitute a large subgroup in the heart failure population.

Further suppression of the RAAS axis using a mineralocorticoid receptor antagonist (MRA) is known to positively influence outcome in HFrEF patients;[30] the clear benefit on cardiovascular outcome was observed in a post hoc analysis of the EMPHASIS-HF trial also in patients with baseline eGFR <60 mL/min per 1.73 m^2.[31] Importantly, MRA trials have generally excluded patients with more advanced CKD (<30 mL/min per 1.73 m^2).

The combination of neprilisyin inhibition on top of on ARB (sacubitril/valsartan) compared with enalapril slowed the rate of decrease in the eGFR and had favourable effects on cardiovascular and renal outcomes, in both HFrEF and HFpEF patients, with and without CKD.[32,33] The mechanisms of relative preservation of eGFR with sacubitril/valsartan are therefore not clear, but might just reflect an improvement in cardiac function.

Contrary to RAAS inhibitors, β-blockers do not cause an acute reduction in eGFR or alter the slope of eGFR decline over time.[34] Post-hoc analysis from trials investigating efficacy showed that patients with the lower GFR actually had the higher beneficial effect of β-blockers.[35–37]

Novel therapeutic regimens with sodium-glucose transporter-2 (SGLT-2) inhibitor may also play a key role in improving outcomes in heart failure patients with CKD. SGLT-2 inhibitors, through the block of sodium/glucose uptake in the proximal tubule, can induce plasma volume contraction and decreasing glomerular hyperfiltration, which leads to better long-term kidney preservation and improves diuretic and natriuretic responses to other diuretic agents. Moreover, SGLT-2 inhibitors might improve the efficiency of myocardial energetics. It has been postulated that the kidney protection and natriuretic effects induced by SGLT-2 inhibitors may account for the reduction in heart failure hospitalization in recent trials,[38] which was greater in patients with worse baseline renal function. Also dapaglifozin was shown to reduced the risk of hospital admission for worsening heart failure, increased survival and improved symptoms in HFrEF patients with and without type-2 diabetes either in patients with CKD and by a similar magnitude in those without CKD.[39] Ongoing trials (DAPA-CKD, EMPA-KIDNEY) will help us to better understand how a nephro-protective effect of these drugs may contribute to preventing progression and adverse outcome in heart failure patients with CKD.

Last, it remains fundamental to consider appropriate treatments for comorbidities often present in cardio–renal syndrome, such as anaemia and acid-base disorder, following established guidelines.[40,41]

Exercise tolerance in patients with heart failure and CKD

The impact of renal dysfunction on exercise capacity has been poorly defined. Cardiopulmonary exercise test (CPET) has been proposed as a valuable tool in CKD.[42] The relation of kidney function to exercise capacity and the impact of impaired renal filtration rate on the prognostic accuracy of maximum rate of oxygen consumption (VO_2 peak) was evaluated in the large Metabolic Exercise Cardiac Kidney Index (MECKI) score database.[43] The major findings of the study were two-fold:

1. Renal function, as assessed by eGFR, correlated with peak VO_2, independent of other established factors influencing exercise capacity, such as age, gender, obesity, New York Heart Association (NYHA) class, atrial fibrillation, haemoglobin, and treatments, including cardiac resynchronization therapy. Peak VO_2 as well as other key CPET-derived variables, including the minute ventilation - carbon dioxide production relationship, significantly worsened with declining renal function (Figure 1).
2. The combinations of cut-off values of eGFR and peak VO_2 allowed to best predict prognosis but

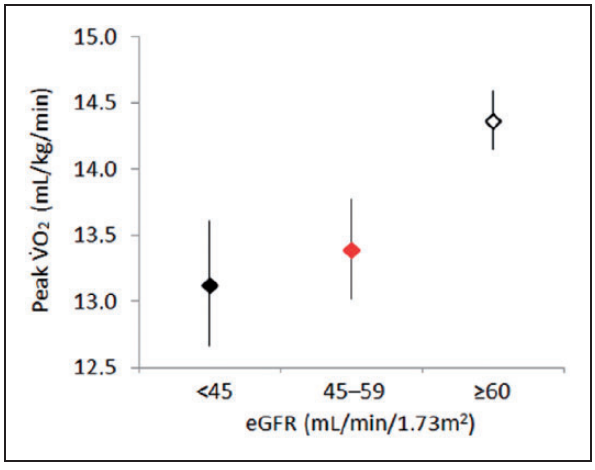

Figure 1. Multivariate adjusted geometric mean peak VO_2 with 95% confidence interval according to strata of estimated glomerular filtration rate (eGFR). (Adapted from Scrutinio et al.[43]) VO_2: maximum rate of oxygen consumption.

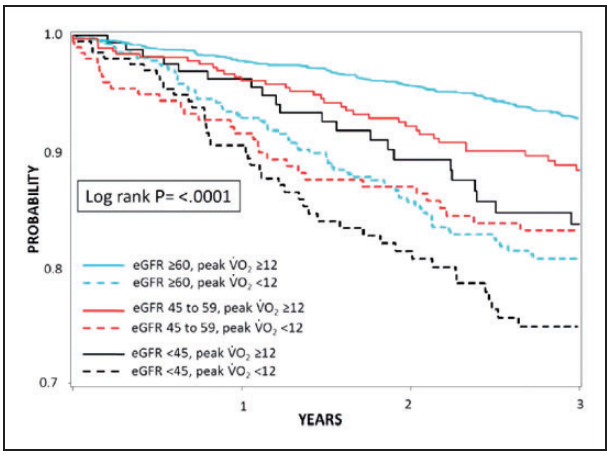

Figure 2. Kaplan–Meier survival curves in the three subgroups of estimated glomerular filtration rate (eGFR), stratified by peak VO_2. (Adapted from Scrutinio et al.[43])
VO_2: maximum rate of oxygen consumption.

testing for interaction was not significant (Figure 2). However, the lack of significant interaction between eGFR and peak VO_2 in relation to mortality prediction suggested that in patients with more severe renal dysfunction, the prognostic weight of other risk markers outranks that of decreased exercise capacity.

The results of this study are consistent with previous observation on the negative impact of renal dysfunction on peak VO_2 in HfrEF.[44,45] Van Laethem et al. studied 79 heart transplantation patients.[45] In this population estimated GFR was a strong independent predictor of decreased exercise capacity. An eGFR value of 53 mL/min per 1.73 m^2 was the optimal cutoff for discriminating patients with a peak $VO_2 <$ or >18 mL/kg per min.

A significant correlation did not prove a cause–effect relationship and, moreover, the association of decreasing peak VO_2 with declining renal function might merely reflect a more advanced stage of heart failure. Nonetheless, it is tempting to speculate about some potential mechanisms which may be the pathophysiological link between exercise performance and renal function. In heart failure, chronic sympathetic activation causes a decrease in the responsiveness of the failing heart to catecholamines, thus limiting its ability to augment cardiac output during dynamic exercise, an increase in peripheral vascular resistance, and an impairment of skeletal muscle vasodilation capacity during exercise leading to muscle hypoperfusion.[46–49] In addition, as reviewed by Middlekauff,[50] chronic sympathetic activation may contribute to skeletal myopathy by inducing abnormalities of excitation–contraction coupling, alterations of metabolism resulting in premature production of lactic acid and reductions of fatigue-resistant oxidative fibres and by indirectly triggering skeletal muscle inflammation leading to activation of catabolic and apoptotic pathways.[50,51]

Renal dysfunction may act as an amplifier of sympathetic activation in heart failure,[46,52–54] potentiating the sympathetically mediated, central and peripheral mechanisms underlying reduced exercise capacity. Notably, the VE versus VCO_2 relationship slope, a strong marker of chemoreflex activation, was higher in the lowest eGFR strata. Grassi et al.[54] demonstrated that sympathetic activation is already detectable in the initial stages of CKD and that the magnitude of the adrenergic drive is proportional to the degree of renal dysfunction.[54] In heart failure, the kidneys behave as both target and source of central sympathetic drive.[52,54] Efferent sympathetic activity to the kidneys enhances renin release, leading to increased angiotensin II production, increases sodium reabsorption and decreases renal blood flow and GFR.[55] Angiotensin II, in turn, exhibits a sympathoexcitatory action.[56] In addition, afferent signals from the dysfunctional kidneys contribute to reflexly increase central sympathetic drive,[57] thus fuelling the vicious circle of sympathetic overactivity. Systemic inflammation with elevated levels of circulating proinflammatory cytokines is a prominent feature both in heart failure and in CKD and may induce proteolysis in skeletal muscle, through activation of ubiquitin–proteasome and myostatin pathways.[57–59] Chronic metabolic acidosis is a common condition in moderate to severe CKD and may worsen catabolic/anabolic imbalance in the skeletal muscle.[57–59] In addition, elevated levels of angiotensin II may contribute to skeletal myopathy by enhancing protein degradation and myocyte apoptosis.[60] Hormonal disorders such as growth hormone and insulin-resistance, oxidative stress and uremic toxins also may contribute.[58,59]

Uric acid

The relationship between serum uric acid and CVD has gained a lot of attention over the years. It was first described in respect to coronary artery disease (CAD), but it soon became obvious that the relationship holds true for different cardiac conditions. Several epidemiological studies have actually found an association between increased serum uric acid levels and elevated vascular event rate and mortality in patients with hypertension, diabetes and prior CVD.[61,62] Hyperuricaemia also predicts mortality and adverse cardiovascular outcome in patients undergoing myocardial revascularization and/or cardiac valve surgery.[63] An elevated uric acid has been proposed as a

potential modifier in Systemic Coronary Risk Estimation (SCORE).

In recent years, there has been growing interest regarding elevated uric acid in heart failure. Current evidence suggests that increased uric acid levels are common in chronic heart failure; high levels of uric acid may be either a marker of poor prognosis, which could be used in conjunction with other risk factors, or an active player in the pathogenesis of heart failure.[64] If it is only a marker, it could be used for monitoring of the course of the disease and guidance of treatment, but if it is an active participant, it may represent a novel and attractive therapeutic target.

Prognostic significance of elevated uric acid in heart failure patients

According to a recent study, about half of patients with heart failure have a serum uric acid (SUA) concentration above the reference upper limit: 43% of heart failure patients with HFrEF and 57% with HFpEF.[65] Elevated SUA predicts morbidity and mortality in mild to moderate as well as advanced cases.[66] Moreover, increasing evidence suggests that moderately elevated SUA levels are independently associated with an increased risk of adverse outcomes both in patients with acute heart failure[67,68] and in patients with chronic heart failure.[68–70] For every 1 mg/dL increase in uric acid the risk of all-cause mortality and the composite endpoint in heart failure increased by 4% and 28%, respectively.[71] Association between moderately elevated uric acid and adverse cardiovascular outcomes was demonstrated also in the GISSI-HF trial.[72] It is interesting to note that this association remained statistically significant even after adjustment for several cardiovascular risk factors, medications and comorbidities, including CKD. Other trials showed that association between uric acid levels and cardiovascular events and heart failure hospitalizations was significant only in patients without kidney failure.[68,69]

More recently, the prognostic value of elevated uric acid in the current clinical practice of heart failure was assessed by a post-hoc analysis of the MECKI (Metabolic Exercise Cardiac Kidney Index) score database, which includes a large optimally treated HFrEF patient population.[73] The main messages from this study were:

1. Uric acid was associated with both cardiovascular and total deaths also in contemporary optimally treated HFrEF population.
2. In particular, uric acid was associated with cardiovascular death and total mortality in patients less severe heart failure, that is, in NYHA class I–II, but not in those with NYHA class III–IV. Similarly, SUA is more strongly associated with death in patients with more preserved exercise performance.
3. After adjustment for several prognostic variables such as peak VO_2, VE/VCO_2 and the MECKI score, uric acid still maintained prognostic power, but in comparison with the MECKI score, the receiver operating characteristic curve analyses showed that SUA did not have added prognostic power both in the general heart failure population and in subgroups of patients with different heart failure severity, according to NYHA class and peak VO_2 (Figure 3).

In more advanced stages of heart failure, the above mentioned confounding factors may play a major contributing role in adverse prognosis thus reducing the role of SUA and consequently with lower correlation between SUA and mortality. Regardless, SUA when added to the MECKI score, has no added prognostic power either in the general population and in heart failure populations of different heart failure severity.

The severity of hyperuricaemia is related to NYHA functional class, to higher maximal oxygen consumption and to the degree of diastolic dysfunction impairment. The highest uric acid concentrations may be observed in patients with advanced chronic heart failure or cardiac cachexia.[74] Elevated uric acid could also be a predictor of development of heart failure in healthy people. In the Cardiovascular Health Study, the incidence of heart failure was 21% in participants with chronic hyperuricaemia and 18% in those without; the results showed that an increase of 1 mg/dL in uric acid conferred a 12% increase in risk of new heart failure.[75] Kim et al. also reported that uric acid levels were independently a better predictor of poor outcome than N-terminal pro B-type natriuretic peptide (NT pro-BNP) in heart failure patients.[76]

Although there is strong evidence of association between elevated uric acid and prognosis in heart failure, biological mechanisms linking hyperuricaemia to poor long-term survival outcomes in patients with heart failure are not fully understood.

Metabolism of uric acid

Uric acid is the final oxidation product of purine catabolism in humans. The reaction involves consecutive conversions of hypoxanthine to xanthine and xanthine to uric acid, which are catalysed by two enzymes, xanthine oxidase (XO) and xanthine dehydrogenase.

Uric acid is produced in the liver. Approximately two-thirds of uric acid is excreted in the urine with the remaining portion undergoing intestinal elimination as faeces.[77] Uric acid is filtered by the glomerulus

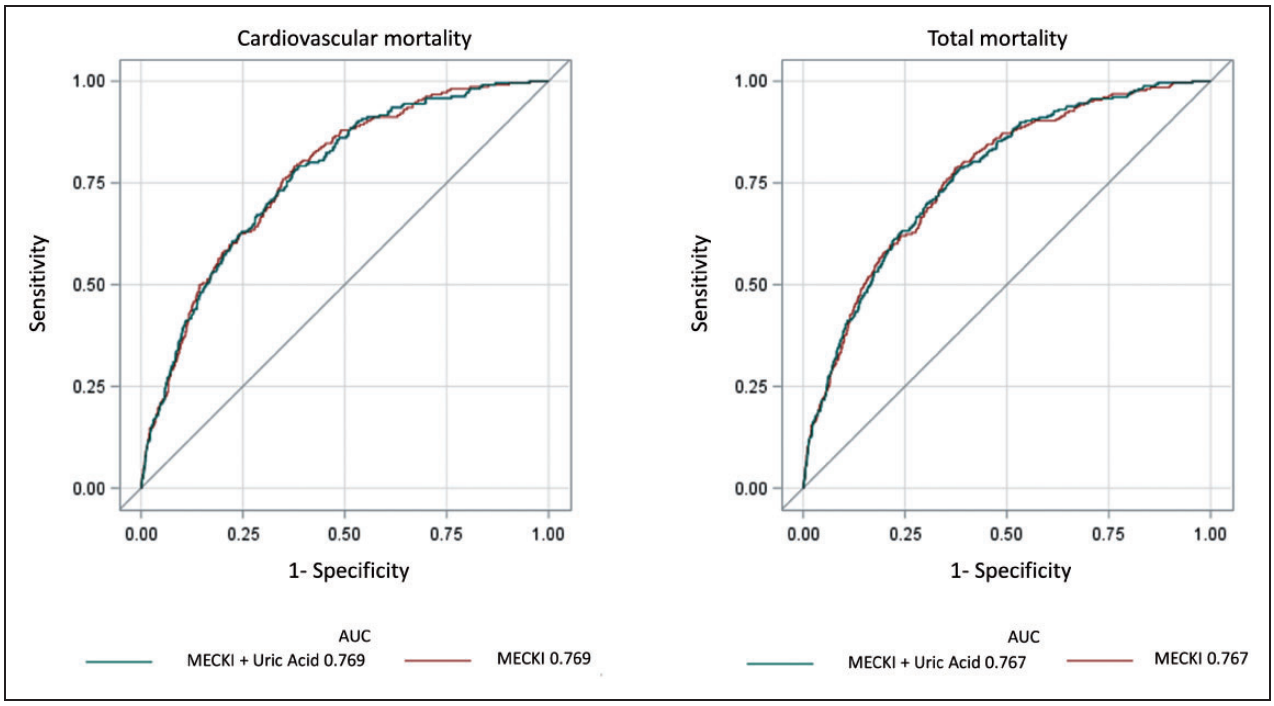

Figure 3. Receiver operating characteristic (ROC) curve for cardiovascular mortality (left diagram) and total mortality (right diagram) for MECKI score and for MECKI score + serum uric acid. Red curve: ROC curve for the MECKI score; green curve: ROC curve for the MECKI score combined with serum uric acid level. (Adapted from Piepoli et al.[73])
MECKI: Metabolic Exercise Cardiac Kidney Index; AUC: area under the curve.

and is secreted in the proximal tubule, where a majority of the filtered and excreted load undergoes reabsorption. Under physiological circumstances, only 5–10% of the filtered uric acid is excreted. Several factors including diet, medications, physiological and pathological conditions participate in regulation of serum uric acid.[78]

In the setting of heart failure, at least two different processes can be responsible for increased uric acid: *increased production* resulting from oxidative stress and *decreased excretion* due to renal insufficiency, which can be a consequence of cardio–renal syndrome and renal congestion.

Uric acid and inflammation

One current theory relating hyperuricaemia and heart failure suggests chronic inflammation may play a role. The pathophysiologic link may be increased XO enzymatic pathway and oxidative stress during states of reduced tissue perfusion and altered metabolic state.[79,80] XO is a potent generator of free radical species; through its activity, which is known to be increased 10-fold in heart failure, XO can induce oxidative stress, which might lead to myocardial remodelling, impaired contractility and fibrosis and decreased cardiac function.[81] XO is also shown to impair the regulation of vascular tone and reduced vasodilator capacity and this could lead to exercise intolerance.[82] In addition, XO can induce the up-regulation of inflammatory cytokines.[83]

Even if high elevated uric acid predicts morbidity and mortality in CVD in general and in heart failure in particular, experimental studies showed that uric acid with its antioxidant properties could be protective against aging, oxidative stress and oxidative cell injury.[77] Therefore, there may be a different explanation for the elevation of uric acid in heart failure.

Uric acid and congestion

A second theory suggests that elevated uric acid levels in heart failure may reflect decreased excretion secondary to impaired renal function, which often accompanies cardiac failure.[84] Furthermore, high levels of lactic acid in heart failure patients, due to cellular hypoxia and consequent change to anaerobic metabolism, are known to decrease uric acid excretion.[85] Uric acid excretion may be further compromised in chronic heart failure (CHF) patients by chronic diuretic use, which produces considerable salt and water loss that stimulates proximal tubule solute reabsorption and subsequent hyperuricaemia.[86,87] Also, increased levels of angiotensin II and norepinephrine seen in heart failure may contribute to increased SUA by stimulating its tubular absorption.[88] Finally, increased uric acid levels

in turn may worsen renal function, creating a vicious cycle. Despite these evidences, the association between hyperuricaemia and poor clinical outcomes of heart failure seems to be more evident in patients with preserved renal function, suggesting a primary role for XO activity and uric acid production in the clinical progression of heart failure.[67–69,72,89]

Uric acid metabolism as a therapeutic target

Although pioneer studies have raised the possibility of preventing heart failure through the use of uric acid lowering agents, namely XO inhibitors and uricosurics, the literature is still conflicting on whether the reduction in uric acid will result in a measurable clinical benefit in heart failure patients.[90]

Most of the accumulated knowledge is related to allopurinol, a XO inhibitor, which is known to rapidly and significantly reduce uric acid level by 1–3 mg/dL, and was demonstrated to improve endothelial function in hyperuricaemic patients with heart failure, presumably via an antioxidant mechanism.[86] The available data are still inconclusive and conflicting. Gotsman et al. reported that allopurinol treatment was associated with improved survival in a large observational cohort of patients with chronic heart failure.[91] Conversely, in the EXACT-HF trial, a 24-week treatment with allopurinol failed to significantly improve survival outcomes in heart failure patients with hyperuricaemia.[92]

Febuxostat was expected to exert a stronger effect on XO inhibition than allopurinol;[93,94] however, data concerning its use in heart failure patients are still contradictory. Cicero et al. demonstrated, in a population of elderly outpatients with heart failure with either reduced or preserved ejection fraction, that cumulative survival was higher in patients treated with febuxostat in comparison with allopurinol treatment.[95] This result largely differs from those of the CARES study, in which the same drugs were compared in a population of obese patients with gout and which reported an increase in the risk of cardiovascular mortality in patients treated with febuxostat.[96] Uric acid lowering agents that act independently of XO have also been studied, with mostly unfavourable results.[86,97]

Recent trials on SGLT-2 inhibitors demonstrated a potential role of these drugs in lowering SUA. This effect seems to be secondary to their inhibition on GLUT9 isoform 2, which is known to exchange glucose for uric acid in the renal proximal tubules and mediate uric acid reabsorption at the collecting ducts of the renal tubules.

In a meta-analysis of 62 clinical trials, treatment with an SGLT-2 inhibitor consistently reduced circulating uric acid concentrations.[98] Reductions in uric acid are generally greater if the HbA1c value is higher, consistent with greater uricosuria accompanying greater glucosuria, but there was no clear difference in the extent of uric acid lowering across the range of 'low-to-high' normal uric acid values. Mean reductions in SUA with empagliflozin were typically marginally, not significantly, greater than those with canagliflozin and dapagliflozin.[98] Thus, the similar lowering of uric acid observed with each of the SGLT-2 inhibitors indicates a class effect, with no substantive differences between agents or doses used routinely in the treatment of type 2 diabetes. However, the specific role of these drugs in uric acid homeostasis and the consequent clinical impact remain unknown.

Given the conflicting data, future large randomized controlled trials are required to better examine the potential advantages of a tailored treatment with drugs reducing uric acid in hyperuricaemic patients with chronic heart failure, in order to improve their long-term prognosis.

Exercise tolerance in patients with heart failure and elevated uric acid

The impact of hyperuricaemia on exercise tolerance has been poorly investigated. Leyver et al.[87] evaluated the relationship between SUA concentrations and the measures of functional capacity obtained through CPET. Fifty-nine patients with a diagnosis of chronic heart failure due to CAD ($n = 34$) or idiopathic dilated cardiomyopathy ($n = 25$) and 20 healthy controls underwent assessment of functional capacity. VO_2 max and SUA were measured during a maximal treadmill exercise test. They reported an inverse relationship between SUA concentrations and VO_2 max in heart failure patients; this link was independent of diuretic dose, serum creatinine, fasting insulin, alcohol intake, body mass index and insulin sensitivity. They concluded that the strong correlation between SUA and VO_2 max suggests that in chronic heart failure, increased SUA concentrations may reflect an impairment of oxidative metabolism; this hypothesis was supported by the finding of a positive correlation between serum uric acid levels VE/VCO_2.

It was also reported that in patients with CHF, SUA concentration is inversely related to the ventilatory anaerobic threshold, independently of the hyperuricaemic effects of renal impairment and diuretic therapy.[99] This relationship could be explained considering the early switch to anaerobic metabolism and consequent accumulation of lactate in heart failure patients' cells. Reduced cellular availability of oxygen, by causing depletion of adenosine triphosphate and accumulation of hypoxanthine and uric acid, could also account

for the observed association between the anaerobic threshold and SUA.

These data suggest that the relationship between increased SUA levels and impairments of exercise tolerance in heart failure could be consequent to derangement of oxidative metabolism. However, a direct role of uric acid cannot be excluded. Langlois et al. found that hyperuricaemia in peripheral arterial disease patients with hypertension was associated with a worse functional status of the peripheral circulation, as evidenced by more pronounced claudication (low absolute claudication distance) on a treadmill test.[100] High SUA levels can cause endothelium injury by increases in platelet aggregation and through a direct pro-inflammatory activity.[101] Uric acid may also stimulate vascular smooth cell proliferation, whereas it reduces nitric oxide availability.[102] Moreover, high uric acid levels significantly increased angiotensin II in cultured endothelial cells and this further prompted endothelial cell senescence and apoptosis.[103]

Finally, elevated SUA levels could lead to endothelial dysfunction, which is known to be a key feature of CHF, contributing to increased peripheral vasoconstriction and impaired exercise capacity.

Declaration of conflicting interests

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