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EXPERT CONSENSUS

Practical management of worsening renal function in outpatients with heart failure and reduced ejection fraction: Statement from a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology

Prise en charge pratique de l'aggravation de fonction rénale chez les patients ambulatoires atteints d'insuffisance cardiaque à fraction d'éjection altérée: position d'un groupe multidisciplinaire d'experts et du Groupe Insuffisance Cardiaque et Cardiomyopathie (GICC) de la Société Française de Cardiologie

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Abbreviations: ACE, angiotensin-converting enzyme ; ARB, angiotensin receptor blocker ; ARN, angiotensin receptor neprilysin ; CI, confidence interval ; CKD, chronic kidney disease ; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration ; eGFR, estimated glomerular filtration rate ; ESC, European Society of Cardiology ; GFR, glomerular filtration rate ; HFrEF, heart failure with reduced ejection fraction ; HR, hazard ratio ; NSAID, non-steroidal anti-inflammatory drug ; RAAS, renin-angiotensin-aldosterone system ; WRF, worsening renal function.

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Renal function is often affected in patients with chronic heart failure with reduced ejection fraction (HFrEF). The complex interplay between heart and renal dysfunction makes renal function and potassium monitoring mandatory. Renin-angiotensin-aldosterone system (RAAS) blockers are a life-saving treatment for patients with HFrEF, regardless of worsening renal function. Uptitration to the maximum-tolerated dose should be a constant goal. This simple fact is all too often forgotten (only 30% of patients with heart failure receive the target dosage of RAAS blockers), and the RAAS blocker effect on renal function is sometimes misunderstood. RAAS blockers are not nephrotoxic drugs as they only have a functional effect on renal function. In many routine clinical cases, RAAS blockers are withheld or stopped because of this misunderstanding, combined with suboptimal assessment of the clinical situation and underestimation of the life-saving effect of RAAS blockers despite worsening renal function. In this expert panel, which includes heart failure specialists, geriatricians and nephrologists, we propose therapeutic management algorithms for worsening renal function for physicians in charge of outpatients with chronic heart failure. Firstly, the essential variables to take into consideration before changing treatment are the presence of concomitant disorders that could alter renal function status (e.g. infection, diarrhoea, hyperthermia), congestion/dehydration status, blood pressure and intake of nephrotoxic drugs. Secondly, physicians are invited to adapt medication according to four clinical scenarios (patient with congestion, dehydration, hypotension or hyperkalaemia). Close biological monitoring after treatment modification is mandatory. We believe that this practical clinically minded management algorithm can help to optimize HFrEF treatment in routine clinical practice.

MOTS CLÉS
Hyperkaliémie ;
Insuffisance cardiaque ;
systolique ;
Maladie rénale chronique ;
Fonction rénale ;

Résumé La fonction rénale des patients insuffisants cardiaques avec fraction d'éjection réduite (IC-rFE) est fréquemment modifiée. Les interactions complexes entre les dysfonctions cardiaques et rénales rendent nécessaires le suivi de la fonction rénale et du potassium. Les bloqueurs du système rénine-angiotensine-aldosterone (BSRAA) diminuent la mortalité des patients IC-rFE indépendamment d'altérations éventuelles de la fonction rénale. L'augmentation à doses maximales tolérées de ces médicaments doit être un objectif constant. Seulement 30% des patients IC-rFE reçoivent des BSRAA à dose maximale et l'effet des BSRAA sur la fonction rénale est parfois mal compris. Les BSRAA ne sont pas néphrotoxiques puisqu'ils n'ont qu'un impact fonctionnel sur la fonction rénale. Dans de nombreuses situations

Syndrome cardio-rénal ; Maladie cardiovasculaire ; Œdèmes d'origine cardiaque

cliniques, les BSRAA sont suspendus ou stoppés à cause de cette incompréhension, d'une évaluation sous-optimale de la présentation clinique et/ou d'une sous-estimation de l'impact en termes de diminution de la mortalité lié à l'utilisation des BSRAA (en dépit de l'aggravation de fonction rénale). Notre groupe d'experts regroupant spécialistes d'insuffisance cardiaque, gériatres et néphrologues propose un arbre décisionnel de prise en charge de l'aggravation de fonction rénale destinés aux médecins prenant en charge les patients IC-rFE ambulatoires. Dans un premier temps, avant d'envisager des modifications thérapeutiques, le contexte clinique doit être pris en compte, notamment la présence de facteurs intercurrents (p.e. infection, diarrhée, fièvre), d'une déshydratation ou de congestion, le niveau de pression artérielle et la prise de médicaments néphrotoxiques. Dans un deuxième temps, nous suggérons que les modifications thérapeutiques soient adaptées à 4 scenarios cliniques (patients congestif, déshydraté, hypotendu ou hyperkaliémique). Un suivi biologique rapproché après les modifications thérapeutiques est indispensable. Nous pensons que cet algorithme clinique et pragmatique peut aider à l'optimisation du traitement des patients IC-rFE en pratique clinique courante.

Background

Renal function is often affected in outpatients with stable chronic heart failure with reduced ejection fraction (HFrEF). Several mechanisms may coexist, including lower blood supply and increased congestion, induced by: heart pump failure; chronic activation of the adrenergic system and the renin-angiotensin-aldosterone system (RAAS); and direct and indirect effects of heart failure (HF) drugs [1]. Renal function may also be affected by age and co-morbidities frequently associated with heart failure, such as atherosclerosis, diabetes and arterial hypertension. Approximately 30% of patients with chronic heart failure have a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 [2].

Inversely, worsening renal function (WRF) has direct and independent consequences on heart failure symptoms and adverse clinical outcomes [3,4]. Although the subject of ongoing debate, WRF is generally defined in clinical studies as a 20—30% decrease in estimated GFR (eGFR) or an increase in creatinine of > 0.3 mg/dL within 15 to 30 days after the intervention [2,5]. Using this definition, WRF is deemed to occur in approximately 25% of cases, with a deleterious effect on outcome [2]. Given this complex interplay between heart and renal dysfunction, it is therefore imperative to monitor renal function in patients with heart failure.

HFrEF-related morbidity and mortality have improved significantly in the past 30 years, as a result of the implementation of effective drug treatments [6]. One of the major drug classes in this field is RAAS blockers, which include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and angiotensin receptor neprilysin (ARN) inhibitors, together with mineralocorticoid receptor antagonists. These drug classes, as well as beta-blockers and diuretics, have a specific effect on renal function [7].

Moderate-to-severe chronic kidney disease (CKD) in patients with heart failure is a major cause of underprescription of RAAS blockade. In heart failure registries, factors significantly associated with underprescription are history of hyperkalaemia and WRF [8—11]. This underprescription or failure to reach the target dose is associated with increased adverse outcomes compared with in patients who receive the full recommended doses [12]. In these registries, only ~30% of all patients with heart failure receive the target dose of RAAS blockers [9]. In addition, in routine practice, the detection of any WRF or hyperkalaemia is a major cause for RAAS blocker dose reduction or suspension [13].

Yet, the absolute benefit of the use of these drugs has repeatedly been shown to remain positive, despite the reduced GFR reported in the various trials on RAAS blockers conducted in outpatients with chronic heart failure and renal dysfunction. The benefit of RAAS blockers is even greater in patients with reduced eGFR than in patients with normal renal function [5,14]. In a recent meta-analysis of major randomized studies exploring the relationship between WRF and RAAS inhibition, WRF was more frequent in patients using RAAS inhibition compared with placebo. However, in patients with HFrEF, RAAS inhibition was less frequently associated with poor outcomes compared with in patients with WRF in the placebo group [3]. Hence, the occurrence of WRF does not eliminate the survival benefit of RAAS blockade compared with placebo [15]. There is therefore compelling evidence to support the prescription of RAAS blockers at the maximum-tolerated dose despite the moderate renal dysfunction that may occur with treatment.

In contrast to the large body of evidence of the benefits of RAAS blockade in HFrEF, the evidence of benefit in heart failure with preserved ejection fraction is a matter of continuing debate [16]. This review will therefore only address outpatients with chronic HFrEF. Of note, acute management is not considered in this review, when each minute counts [17].

In this expert panel, comprising heart failure specialists, geriatricians and nephrologists, we review the pathophysiology of WRF, and propose targeted therapeutic-management algorithms for physicians treating outpatients with chronic heart failure—a setting that remains a persisting critical concern.

Pathophysiology of WRF in patients with chronic heart failure

Recent reviews have focused in detail on the pathophysiology of renal dysfunction during heart failure [18]. In patients with chronic heart failure, a number of different mechanisms can induce WRF. Most cases are related to

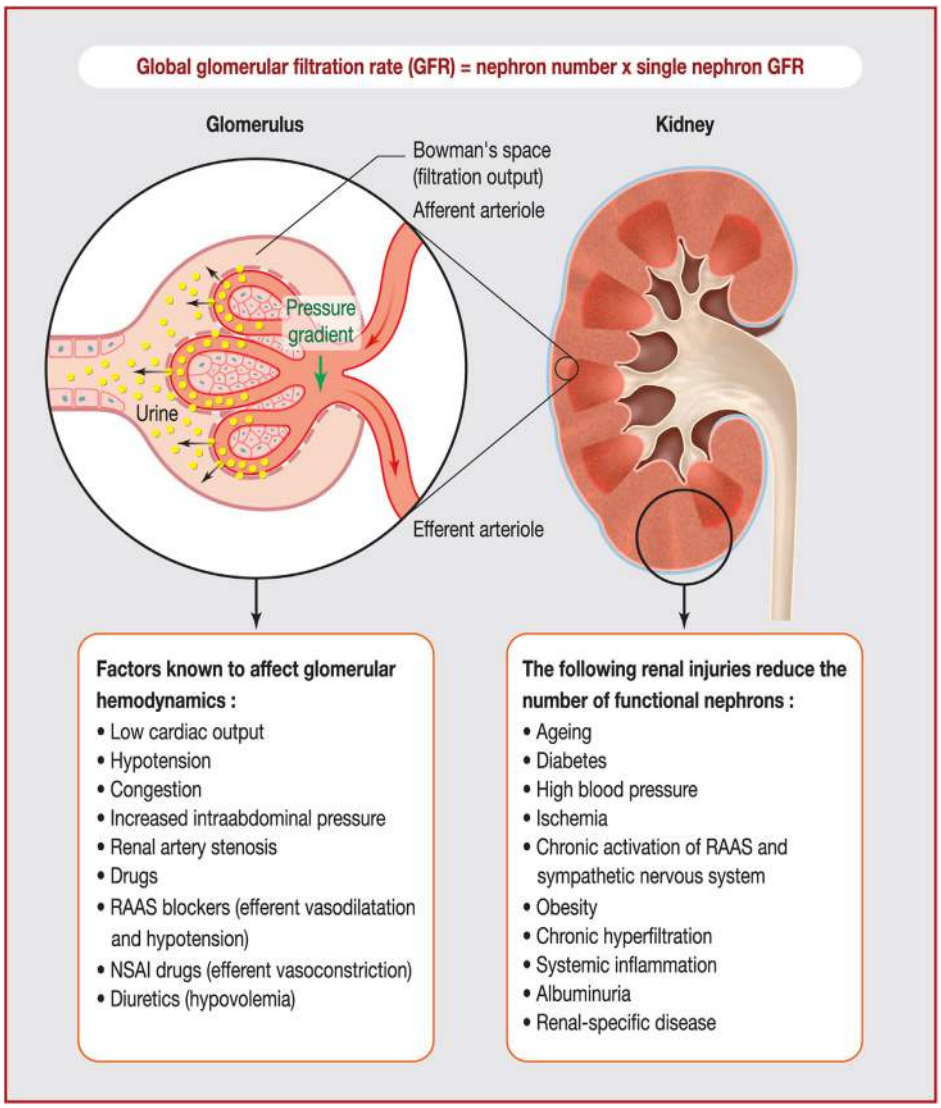

Figure 1. Main factors influencing glomerular filtration rate (GFR) in patients with chronic heart failure. RAAS: renin-angiotensin-aldosterone system; NSAI: non-steroidal anti-inflammatory.

changes in extracellular volume and blood pressure: congestion, hypotension and dehydration are the main drivers of WRF in patients with heart failure. All of these mechanisms are summarized in Fig. 1. Importantly, other causes of renal dysfunction should also be systematically investigated, including urinary obstruction.

In healthy subjects, renal perfusion remains stable when the mean blood pressure is as low as 60 mmHg, because of autoregulation. A sufficient pressure gradient within the glomerulus is essential to maintain adequate filtration (Fig. 1). This gradient is dependent on glomerular hydrostatic pressure, oncotic pressure and pressure within Bowman's space [19].

Congestion

Congestion is a major factor for WRF in patients with chronic heart failure [20], and is often an underestimated clinical variable. In a cohort of 145 patients with a mean left ventricular ejection fraction of 20%, who were admitted for acute decompensated heart failure, higher central venous pressure was strongly associated with a greater risk of in-hospital WRF. In contrast, no association was found with blood pressure levels, cardiac output and pulmonary wedge pressures. This result was confirmed in the ESCAPE trial, in which only right atrial pressure was correlated with baseline renal function [21].

Moreover, in studies using renal venous Doppler to assess renal perfusion patterns in patients with acute heart failure [22], renal haemodynamics were clearly shown to improve with decongestion. Conversely, intravascular volume expansion resulted in a significant blunting of renal venous flow, causing WRF [23]. As a result of increased renal venous pressure, renal interstitial pressure rises above hydrostatic pressure [24]; this results in tubular collapse, with an increase in tubular pressure that, in turn, decreases the net ultrafiltration pressure, thereby resulting in decreased renal filtration [25].

Finally, in patients with heart failure, persistent congestion combined with WRF is significantly associated with

Table 1 Clinical features differentiating congestion-related from dehydration-related worsening renal function in patients with heart failure.

	Congestion	Dehydration
Clinical history	Progressive dyspnoea, orthopnoea, weight gain, oedema, cardiac arrhythmia, etc.	Fever, high air temperature, loss of appetite, nausea, digestive loss
Recent drug and dietary changes	Reduction in diuretic dose, NSAIDs, increase in salt intake	Increase in diuretic dose, low salt intake
Weight	Increased	Reduced
Oedema	Present in lower limbs	Absent
Diuresis	Oliguria	Oliguria
Signs of HF	Jugular turgescence, hepatalgia, pulmonary crackles, pleural effusion, etc.	Absent
Blood pressure	Normal or low	Normal or low, orthostatic hypotension
Heart rate	Increased	Increased
Biological data		
Plasma	Increased natriuretic peptides compared with ''dry'' weight baseline value, haemodilution	Haemoconcentration (increased protein concentration and haemoglobin/haematocrit)
Urine	Low sodium excretion (< 20 mmol/L)	Low sodium excretion (< 20 mmol/L)
Echocardiography	High CVP, dilated vena cava diameter (> 21 mm)	Low CVP, flattened vena cava (< 21 mm) and vena cava collapsus during inspiration

CVP: central venous pressure; HF: heart failure.

adverse outcomes compared to WRF without congestion [26].

Dehydration/hypovolaemia

Dehydration is a common occurrence in patients with heart failure. Dehydration is mostly the consequence of excessive diuretic treatment, and is more frequently observed in elderly patients with heart failure (mainly heart failure with preserved ejection fraction) [27]. Dehydration leads to renal hypoperfusion and prerenal renal failure. Prerenal renal failure is characterized by an intact renal parenchymal function with renal hypoperfusion. Dehydration can also result from external clinical settings, such as insufficient hydration, external heat with increased sweating, fever and gastrointestinal disorders. Dehydration or hypovolaemia directly affects renal blood flow and consequently reduces GFR accordingly. Clinical features differentiating congestion from dehydration are summarized in Table 1.

Hypotension

Most heart-failure drugs have a direct and significant hypotensive effect. Renal blood flow can thus be directly affected as a result of heart-failure treatments and altered autoregulation in patients with CKD, caused by structural remodelling of the vascular wall and vascular hyalinization [19]. However, in clinical studies, the link between systolic blood pressure and WRF remains weak [2,20]. Hypotension is nevertheless a major barrier to optimal medical treatment in outpatients with heart failure [9,10].

Nephrotoxic drugs

Nephrotoxic drugs cause glomerular and/or nephron damage, as opposed to the reversible haemodynamic effects induced by non-steroidal anti-inflammatory drugs (NSAIDs) and RAAS blockers. The renal toxicity mechanisms of NSAIDs are multiple and complex (haemodynamic for acute effects, immunoallergic, podocyte toxicity, etc.). Contrast-induced nephropathy and anti-infectious drugs are possible causes of WRF. Most importantly, drug dose adjustment is mandatory with regard to kidney function.

Drugs with renal haemodynamic effects

NSAIDs or selective cyclo-oxygenase 2 inhibitors induce WRF by blunting the vasodilatory effect of prostaglandin E2; this results in an afferent glomerulus arteriole vasoconstriction, inducing a decrease in both renal blood flow and GFR.

RAAS blockers are non-nephrotoxic and, conversely, have a predictable effect that has been described in various studies in heart failure [4,14,28]. In most randomized controlled studies, introduction of RAAS blockade was associated with a mean 3 ± 4 mL/min/1.73 m^2 decrease in GFR. RAAS blockers reduce the vasoconstrictor effect of angiotensin II on the efferent arteriole. This effect induces a decrease in GFR related to the lower pressure gradient

within the glomerulus. The effect is rapidly reversible after treatment suspension.

The apparent WRF associated with RAAS prescription has been well documented in the literature. In the SOLVD trial, this impairment in renal function following the introduction of ACE inhibitors was neutrally associated with outcome (adjusted hazard ratio [HR] 1.0, 95% confidence interval [CI] 0.8—1.3; $P = 1.0$); conversely, a similar impairment was significantly associated with worse outcome in patients randomized to placebo (adjusted HR 1.4, 95% CI 1.1—1.8; $P = 0.004$) [29]. In the same analysis, patients who continued to receive the study drug despite early WRF still had a significant survival benefit with enalapril therapy (adjusted HR 0.66, 95% CI 0.5—0.9; $P = 0.018$). Consequently, although RAAS blockers can reduce GFR, this reduction is not associated with worse outcome, and the benefit of heart-failure treatment remains significant.

Recently, a new ''kid on the block'' with direct renal effects has appeared in the field of heart failure. Sodium-glucose co-transporter 2 inhibitors reduce the glomerular hyperfiltration that is present in patients with diabetes and reduce heart-failure events, with better protection of renal function in patients with HFrEF. In the DAPA-HF study, dapagliflozin significantly reduced cardiovascular death and heart-failure events without an increase in WRF compared with placebo. Further evidence-based randomized trials and ''real-world'' data are needed to better understand the benefits of this new heart-failure therapy and its effect on renal function [30].

Populations at risk of developing WRF

High-risk patients are those with atherosclerotic cardiovascular disease, pre-existing CKD, diabetes, volume depletion, hypotension or renal artery stenosis. Elderly patients deserve special attention as they are particularly at risk of developing WRF, as a consequence of several factors. These include the progressive decline in renal function (nephron loss), increased co-morbidities, more advanced heart failure, polymedication (with its associated risk of interaction), overuse of inappropriate drugs and underutilization of effective treatments [31,32].

Assessing renal function in patients with HF

The accurate assessment of renal function is a challenging task in patients with chronic heart failure for several reasons. First, GFR estimation equations have all been validated for use in a steady-state setting, which is not always the case in heart failure. In haemodynamically unstable conditions, intraindividual variations in serum creatinine are much more meaningful, and should remain the gold standard for detecting acute and subacute renal dysfunction.

Second, even in the context of relative cardiorenal stability, GFR assessment with creatinine-based equations is suboptimal. This is partly because malnutrition and sarcopenia are frequent in this setting. The presence of sarcopenia in patients with heart failure induces an overestimation of GFR. In this regard, serum cystatin C, known to be less dependent on muscle mass than serum creatinine, could be an appealing alternative [33]. In effect, the GFR-estimation equation using cystatin C values is more robust than the classical creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. However, at this juncture, it appears too early to recommend the widespread use of cystatin C. Therefore, the best GFR assessment method in patients with heart failure in the outpatient setting is currently the CKD-EPI equation. Indeed, this formula has been shown to be reliable, despite its numerous limitations. It should, nonetheless, be used with caution in the elderly and/or in case of malnutrition, as its measurement results overestimate true renal function. For drug-dosing adjustment, many experts advocate specifically using the Cockcroft-Gault formula, which was used in drug trials to define the study population. This should be balanced with the fact that ''weight'', a particularly fluctuating and confounding variable in patients with heart failure, is integrated into the formula.

In any event, when a patient with heart failure presents with significant renal dysfunction (GFR < 45 mL/min), they should be considered for referral to a nephrologist for management optimization. Rapid referral to a nephrologist is also mandatory in instances of: an increase in creatinine concentration > 100% of the reference value; a new decrease in eGFR $\leq$ 20 mL/min/1.73 m^2; and persistent hyperkalaemia > 5.5 mmol/L despite adequate therapeutic management.

Initiation and titration of ACE inhibitors, ARBs, ARN inhibitors and mineralocorticoid receptor antagonists

The first introduction of RAAS blockers to a patient is critical. Whether this initial introduction is performed in hospital or in the outpatient clinic, the goal is to reach the maximum-recommended dose or, if unfeasible, the maximum-tolerated dose. The beneficial effects of RAAS blockers are probably dose dependent [34]. High doses of RAAS blockers can be prescribed in patients with CKD as in the general population, albeit with closer clinical and biological follow-up. In most cases, WRF should not be a limitation to the titration of beta-blockers.

Titration can be performed by various means depending on the patient's history, clinical situation (blood pressure, congestion) and, naturally, baseline renal function. In general, a progressive slow titration without therapeutic inertia is the recommended course of action: double the dose every 1—2 weeks. Ideally, the patient's symptoms (symptomatic orthostatic hypotension), blood pressure (including standing blood pressure) and renal function should be monitored at each step.

A blood-screening test should be performed 1 week after each introduction or titration; serum creatinine and blood potassium should be assessed at every step before increasing dosage. At each titration visit, the patient and their family should be educated regarding signs of dehydration, hypotension and weight. Information about ideal water and salt intake according to the weather/temperature or physical activity should also be provided as often as possible.

As the titration of RAAS blockers occurs concomitantly with the titration of beta-blockers, the sequence in the modification of heart-failure drugs should be anticipated. Usually, the increase in the dosage of beta-blockers parallels the increase in the dosage of RAAS blockers, to avoid having a high dose of one treatment and a low dose of the other. This is mostly a pragmatic approach, as these drugs have demonstrated beneficial effects that result from actions on different pathophysiological pathways. In addition, in the 2016 European Society of Cardiology (ESC) guidelines [7], mineralocorticoid receptor antagonist initiation follows ACE inhibitor/ARB and beta-blocker titration.

In patients without clinical signs of congestion, downtitration of diuretics may favour the titration of RAAS blockers [35] and beta-blockers.

The following at-risk situations should prompt careful clinical follow-up: recent hospitalizations with intense diuresis (weight loss > 4 kg); other causes of dehydration (gastrointestinal disorders, fever, heatwave); elderly (aged > 80 years); diabetes; and previous renal failure (baseline GFR < 60 mL/min/1.73 m^2).

Facing WRF in an outpatient with chronic heart failure

General considerations

We assume that every physician is familiar with the basic and stable status of each patient with HF: renal function status, usual weight (ideally ''dry'' weight) and last dosage of heart-failure drug prescriptions (diuretics, RAAS blockers, beta-blockers). Clinical inertia is a major issue. Therefore, once the clinical situation is stabilized, these heart-failure drugs should be uptitrated to the maximum-tolerated dose.

In case of WRF, guidelines from expert task forces have been published by the ESC group (in the supplementary appendix of the guidelines) [7]. These guidelines were based on interpretation of available evidence from different randomized clinical trials and registries. None of the recommended thresholds has been assessed in randomized clinical trials. These guidelines can be summarized in three general rules:

- an increase in creatinine concentration after RAAS blocker initiation is frequent, and is acceptable up to 50% above baseline value; in the same manner, an increase in potassium to $\leq$ 5.5 mmol/L is acceptable;
- for increases in creatinine > 50% and below 100% of the baseline value, the clinical situation should be assessed using a systematic approach (congestion, dehydration, blood pressure, concomitant interaction), and medication should be adjusted accordingly (halving of usual doses can be considered) (see Fig. 2); apply careful and close follow-up after any strategy change; and
- if potassium rises to > 5.5 mmol/L or creatinine increases by > 100% of baseline or is > 310 μmol/L or GFR is < 20 mL/min/1.73 m^2, current ACE inhibitors (or ARBs or ARN inhibitors) and mineralocorticoid receptor antagonists should be stopped, and specialist advice from a nephrologist should be sought; in all instances of hyperkalaemia > 5.5 mmol/L, a second blood sample should be taken for verification, because of potential confounders, such as haemolysis.

Table 2 Main clinical settings requiring urgent hospitalization.

Increase in creatinine > 100% or underlying CKD with acute decrease in eGFR to < 20 mL/min/1.73 m^2
Acutely decompensated HF
Severe ionic disorders, such as hyponatraemia < 125 meq/L, hypokalaemia < 3 mM or hyperkalaemia > 6.0 mM (after verification with a second sample)
Severe dehydration with symptomatic hypotension
Suspicion of cardiogenic shock
Any clinical signs of haemodynamic instability with urinary tract issues (obstruction/infection)
Failure of 48-hour outpatient treatment

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure.

While these general principles are pragmatic, they are, nonetheless, associated with low levels of evidence [36]. From theory to practice in outpatients, our purpose in the following paragraphs is to set out a pragmatic, simple and systematic management algorithm in various clinical settings for clinicians faced with WRF in an outpatient with chronic heart failure.

Urgent hospital referral

The first practical step is to determine which patients require hospitalization. From our consensus panel, the clinical settings in which the physician should consider patient referral as soon as possible to an emergency department, ideally to a hospital with expertise in heart-failure management, are summarized in Table 2.

Clinical aggravating factors such as daily furosemide (or equivalent) > 250 mg/day, issues with adherence and isolation, frailty and lack of autonomy should also be considered.

Clinical/biological assessment of WRF

Before making any decision regarding treatment, it is essential to carefully assess the clinical context of WRF. This approach has recently been suggested by Clark et al., albeit using a different segmentation of clinical settings [36]. According to our consensus panel, the essential variables to take into consideration before changing treatment are as follows (Fig. 2):

- clinical context—any concomitant disorder that could alter renal function status (infection, diarrhoea, hyperthermia, acute heart-failure decompensation, urinary tract pathology), drugs (NSAID introduction) and diet adherence;
- congestion (Table 1)—increase in weight, orthopnoea, jugular distension, lower limb oedema, increase in natriuretic peptide concentrations, decrease in haemoglobin/haematocrit, ultrasound variables showing pulmonary congestion (increased left ventricular

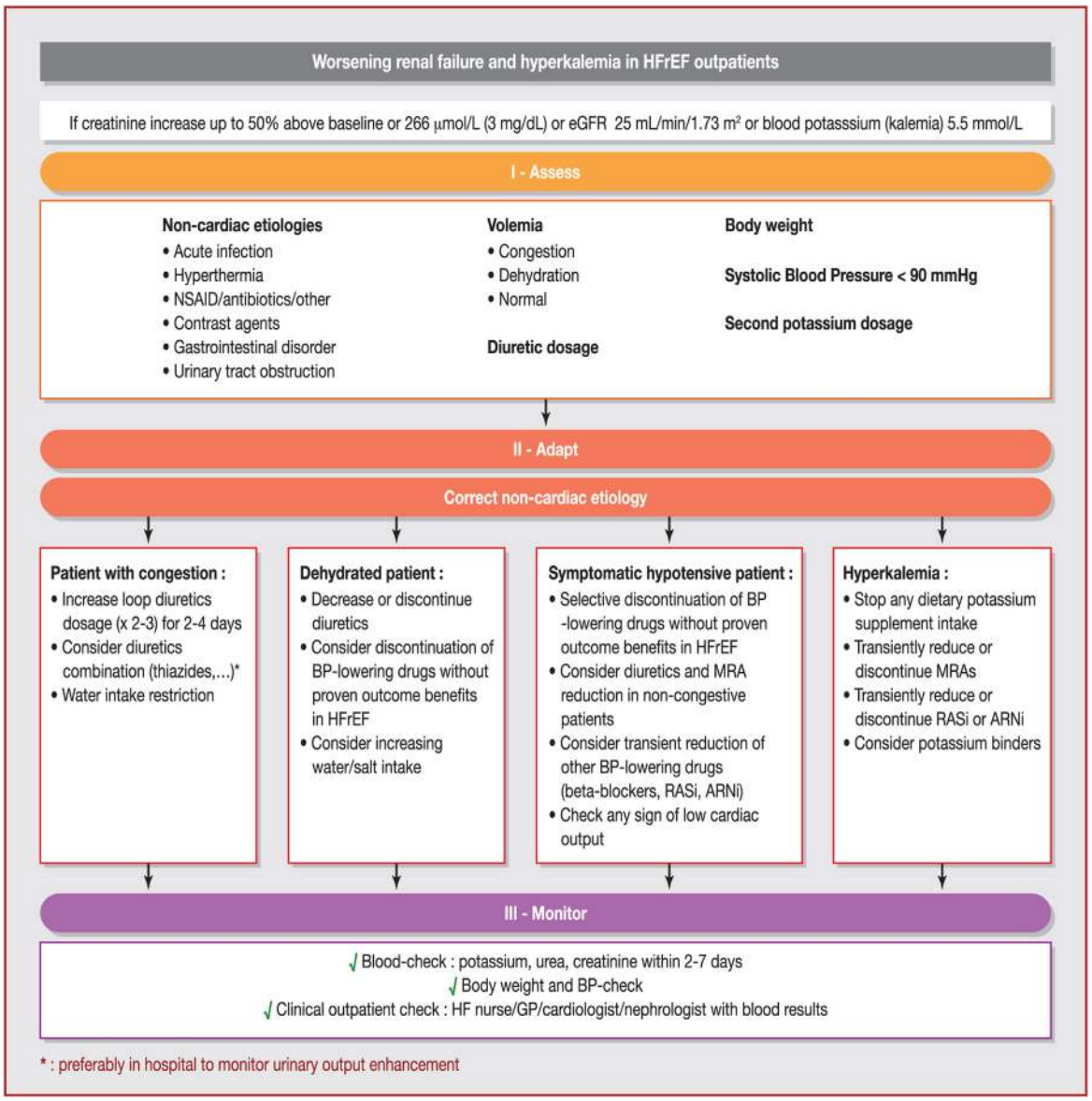

Figure 2. ''Assess, Adapt, Monitor'' (A2M) algorithm for the management of patients with HFrEF and worsening renal function and/or hyperkalaemia. ARNi: angiotensin receptor neprilysin inhibitor; BP: blood pressure; eGFR: estimated glomerular filtration rate; GP: general practitioner; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist; NSAID: non-steroidal anti-inflammatory drug; RASi: renin-angiotensin system inhibitor.

end-diastolic pressure) and systemic congestion (raised right atrial pressure) [37];
- blood pressure—symptomatic hypotension, orthostatic hypotension;
- diuretic dose and clinical signs of dehydration;
- nephrotoxic drugs—NSAIDs, contrast media, antibiotics, human immunodeficiency virus (HIV) drugs;
- potassium supplements—salt diet, bananas, chocolate, low-salt substitute; review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalaemia (potassium-sparing diuretics, e.g. amiloride and triamterene; potassium supplements, e.g. potassium chloride, herbal supplements, etc.)

Practical considerations for WRF management according to clinical setting

All of these considerations are summarized in Fig. 2.

Congestion

In cases of WRF with congestion, diuretic doses should be increased. The 24-hour oral dose of loop diuretics should be significantly increased for 2 to 3 days, i.e. 2 to 3 times the daily dose. The efficacy of such a transient increase should be verified with improvement in the patient's symptoms as well as weight loss, with ''dry'' weight recovery.

Renal potassium should be checked within 7 days following the increase in dosage.

Patients with chronic heart failure may develop resistance to loop diuretics, requiring an increase in dose to maintain diuresis. Spreading the diuretic dose over two to three dosings a day helps to prevent this resistance. When a patient develops resistance to a particular loop diuretic, switching to another with higher bioavailability (e.g. furosemide to bumetanide or torasemide) may improve resistance issues [38,39]. A combination of diuretic classes (loop diuretics with thiazide diuretics) can be used in chronic patients, although this combination must be closely monitored (creatinine, potassium and sodium) especially in the first month. In addition, a variation in the route of diuretic administration may be necessary to overcome diuretic resistance. Intravenous administration of a loop diuretic avoids possible uncertainties regarding intestinal absorption, and ambulatory administration of IV loop diuretics has become another option in recent years [39,40].

The goal is to achieve the patient's usual ''dry'' weight together with improvement in heart-failure symptoms. After achieving this target weight, creatinine and blood potassium must be monitored during the following 7 days, as they may worsen with a slight delay. A closer laboratory follow-up may be suggested in case of severe renal dysfunction (eGFR < 30 mL/min/1.73m^2) or high 24-hour doses of furosemide (i.e. > 250 mg/day). Hyperkalaemia as well as hypokalaemia must be investigated and corrected.

In case of absence of significant improvement within 7 days of an increase in ambulatory diuretic dose, patients should be referred for hospitalization.

Dehydration/hypovolaemia

In this instance, WRF is directly related to ''true'' hypovolaemia, which is secondary to either excessive diuretic-related depletion or dehydration from other causes, such as vomiting, diarrhoea or fever.

Management is incremented according to severity (see Table 2). In less severe cases, management must be personalized in this outpatient setting: downtitrate or discontinue diuretics, including mineralocorticoid receptor antagonists, in most cases; in cases of previous diuretic combination, first suspend thiazide alone; maintain RAAS blockers at the same dose or a 50% decrease in dose, maintain beta-blockers; alleviate low-sodium diet; blood test within 7 days and carry out a new assessment. If there is improvement, consider pursuing diuretic at same downtitrated dosage (a repeated blood test should be performed 48 or 72 hours later); if there is stability, make no change and blood test 48 hours later; if there is worsening, discontinue diuretics and RAAS blockers and increase rehydration, blood test the following day and discuss immediate hospitalization. Therapeutic education of the patient and their relatives is essential in all cases.

Symptomatic hypotension

Prescription of all cardiological treatments without proven outcome benefits in HFrEF (nitrates, calcium blockers) and non-cardiologic hypotensive drugs (alpha-blockers, anti-parkinson drugs, phosphodiesterase inhibitors, etc.) should be re-evaluated. Second, in the absence of concomitant congestion, diuretic doses should also be decreased, sodium restriction alleviated, and (oral) hydration increased. The presence of dysautonomia should be investigated, particularly in patients with diabetes. A decrease in RAAS blocker/ARNi/beta-blocker dose should be considered only after the latter changes. According to the ESC registry data [9], hypotension is more frequently the reason for non-prescription/underdosing of ACE inhibitors/ARBs (67.5%/26%) than beta-blockers (27.9%/17%). As a consequence, downtitration of RAAS blockers rather than beta-blockers may appear appropriate in the context of symptomatic hypotension with WRF, unless patients have a low heart rate. The magnitude of the downtitration should be personalized to the level of hypotension and WRF, as well as to the patient's characteristics.

Regardless of the change applied to drug prescription, patients with hypotension should be reassessed. If hypotension is resolved, reassessment of heart-failure drugs should be performed, and uptitration should be reinitiated if the patient is not at target doses.

Hyperkalaemia

Hyperkalaemia, which is a potential life-threatening condition because of its conduction disturbance properties [41], is an inherent risk associated with RAAS blocker use. In order to achieve the best benefit associated with RAAS blocker use, as demonstrated in clinical trials, it is of utmost importance to adhere to contraindications related to kidney function and serum potassium [42]. According to these guidelines, potassium concentrations can be tolerated up to 5.5 mmol/L in a stable patient with chronic heart failure. Furthermore, it should be remembered that mineralocorticoid receptor antagonist introduction is often associated with a significant increase in potassium concentration, e.g. approximately 0.5 ± 0.2 mmol/L for 25 mg of spironolactone daily.

In all cases, appropriate monitoring is warranted. Beyond baseline assessment, creatinine and potassium concentrations should be reassessed within 1 week of the initial dose, with any dose titrations or with any alterations in other concomitant drugs, diseases or acute illnesses prone to influence potassium concentrations or induce WRF. On a routine basis, potassium and serum creatine should be monitored monthly for the first 3 months, then regularly at 3- to 4-month intervals [43].

Once the diagnosis of hyperkalaemia is confirmed (i.e. pseudohyperkalaemia is ruled out), a ''significant'' hyperkalaemia, associated or not with WRF, should prompt a reappraisal of concomitant drug prescription (e.g. withdrawal of all potassium supplements, such as potassium chloride, or salt substitutes, non-steroidal anti-inflammatory drugs or other nephrotoxic drugs). This may also warrant the temporary downtitration or discontinuation of mineralocorticoid receptor antagonists first. Then, in a second step, reduction or discontinuation of RAAS blockers/ARN inhibitors could be considered [7].

The conjunction of hyperkalaemia and WRF should prompt cardionephrological interactions, and should target the restauration of renal function (as hyperkalaemia may be secondary to the WRF).

The availability of new potential binders (e.g. patiromer or sodium zirconium cyclosilicate) may, however, offer

Table 3 Essential practical rules for renin-angiotensin-aldosterone system blocker management in elderly patients (aged ≥ 80 years).

eGFR is usually overestimated because of sarcopenia
Orthostatic hypotension is frequent and associated with poor outcome; diuretic dose reduction and/or vasodilator downtitration may be advocated
Pay attention to frailty, cognitive disorders and polymedication
Monitor congestion closely after diuretic dose increase; diuretic dosage should be carefully re-evaluated after normalization of volaemia

eGFR: estimated glomerular filtration rate.

new opportunities to overcome hyperkalaemia. The ongoing DIAMOND trial will determine whether the use of these medications improve cardiovascular outcome (ClinicalTrials.gov Identifier: NCT03888066). For the time being, potassium binders may be considered when hyperkalaemia is the main issue to treat and renal function remains acceptable; they can be useful to stabilize and treat hyperkalaemia between 5.5—6 mmol/L allowing maintenance of RAAS blocker treatment [44]. However, careful renal function and blood potassium monitoring is mandatory in this setting.

Specificities in the elderly/very elderly

Elderly patients (particularly those aged > 80 years) deserve special attention. Heart failure is highly prevalent in these patients. Beyond ineluctable age-related nephron loss, most of the aforementioned factors that may precipitate WRF often co-exist in elderly patients. This population is consequently at higher risk of combined heart failure and renal dysfunction. In addition, polymedication, which is frequent in this population, further increases the risk of WRF and hyperkalaemia through nephrotoxic drug interactions. In addition, these patients may experience persistent oedema while exhibiting hypovolaemia during aggressive diuretic treatment, possibly because of delayed vascular refilling.

Lastly, this patient population has often been excluded from randomized clinical trials, therefore RAAS blocker use is more supported by registry data. Table 3 summarizes the key practical recommendations that should be applied in this frail population.

Conclusions

RAAS blockers are a life-saving treatment in patients with HFrEF, regardless of WRF. Uptitration to the maximum-tolerated dose should be a constant goal. This simple fact is all too often forgotten, and the RAAS blocker effect on renal function is commonly misunderstood. RAAS blockers are not nephrotoxic drugs. In many routine clinical cases, RAAS blockers are withheld or stopped because of this misunderstanding, combined with poor assessment of the patient's clinical situation. In the management of patients with chronic HFrEF, monitoring of renal function and blood potassium is just as important as complete clinical assessment of the patient. Each patients with heart failure needs holistic evaluation of all clinical and paraclinical variables in order to determine the most beneficial drug combination in terms of individual benefits and risks.

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