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Practical Management of Worsening Renal Function in Reduced Ejection Fraction Heart Failure Outpatients: Statement from a Panel of Multidisciplinary Experts and the Heart Failure working group of the French Society of Cardiology.

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Conflict of interest

Dr. Legrand reports personal fees from Baxter, Fresenius, Shingotec, Novartis. Dr. Juillard reports grants and personal fees from Baxter, Hemotech, and Amgen, personal fees from Novartis, Vifor and Novo. Dr Courivaud, Isnard, Logeart, Maria, Meune, and Sebbag report personal fees from Novartis. Dr. Rossignol reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa, and is the cofounder of CardioRenal, a company developing a telemonitoring loop in heart failure (including potassium measurements). The authors acknowledge technical support from Novartis for illustrations.

Abstract

In chronic heart failure with reduced ejection fraction (HFrEF) patients, renal function is often affected. 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 of HFrEF patients, regardless of worsening renal function. Uptitration to maximal tolerated dose should be a constant goal. This simple fact is all too often forgotten (only 30% of HF patients receive target dosage of RAAS blocker drugs) and RAAS blocker effect on renal function is sometimes misunderstood. RAAS blockers are not nephrotoxic drugs as they only have a functional impact on renal function. In many routine clinical cases RAAS blockers are withheld or stopped because of this misunderstanding, in combination with a suboptimal assessment of the clinical situation and underestimation of RAAS blockers life-saving effect despite worsening renal function.

In this expert panel including HF specialists, geriatricians and nephrologists, we propose therapeutic management algorithms of worsening renal function for the physicians in charge of chronic HF outpatients. At first, the essential parameters to take into consideration before changing treatment are the presence of concomitant disorders that could alter renal function status (e.g. infection, diarrhea, hyperthermia), the congestion/dehydration status, blood pressure and nephrotoxic drugs intake. In a second step, physicians are invited to adapt medication according to 4 clinical scenarios (patient with congestion, dehydration, hypotension or hyperkalemia). Close biological monitoring after treatment modification is mandatory. We believe that this practical clinically-minded management algorithm can help HFrEF treatment optimization in routine clinical practice.

Introduction

Renal function is often affected in outpatients with stable chronic heart failure and reduced ejection fraction (HFrEF). Several mechanisms may coexist, including lower-blood supply and increased congestion induced by i) heart pump failure, ii) chronic activation of adrenergic and renin-angiotensin aldosterone systems, and iii) direct and indirect effects of heart failure drugs¹. Renal function may also be affected by age and comorbidities frequently associated with heart failure such as atherosclerosis, diabetes or arterial hypertension. Approximately 30% of chronic heart failure patients display a glomerular filtration rate (GFR) below 60 ml/min/1.73m²².

Inversely, WRF has direct and independent consequences on heart failure symptoms and adverse clinical outcomes^{3,4}. Although still the subject of debate, WRF is generally defined in clinical studies as a 20-30% decrease in eGFR, or an increase in creatinine >0.3 mg/dL within 15 to 30 days after intervention^{2,5}. Using this definition, WRF is deemed to occur in approximately 25% of cases with deleterious impact on outcome². Given this complex interplay between heart and renal dysfunction, it is therefore imperative to monitor renal function in patients with HF.

HFrEF-related morbidity and mortality have significantly improved in the last thirty years as a result of the implementation of effective drug treatments⁶. One of the major drug classes in this field are renin-angiotensin-aldosterone system (RAAS) blockers. These include angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs) and angiotensin receptor neprilysin inhibitors (ARNIs) together with mineralocorticoid receptor antagonists (MRAs). These drug classes, as well as beta-blockers and diuretics, have a specific impact on renal function⁷.

Moderate to severe chronic kidney disease in HF patients is a major cause for the under-prescription of RAAS blockade. In heart failure registries, factors significantly associated with under-prescription are history of hyperkalemia and WRF⁸⁻¹¹. This under-prescription or failure to reach the target dose is associated with increased adverse outcomes comparatively to patients reaching the full recommended doses¹². In these registries, only ~30% of all HF patients receive the target dose of RAAS blocker drugs⁹. In addition, in routine practice, the detection of any renal function worsening or hyperkalemia is a major cause for RAAS blocker dose reduction or suspension¹³.

Yet, the absolute benefit of the use of these drugs has repeatedly been shown to remain positive despite the reduced glomerular filtration rate reported in the various trials on RAAS blockers conducted in chronic heart failure outpatients with renal dysfunction. The benefit of RAAS blockers is even greater in patients with reduced eGFR compared to patients with normal renal function^{5,14}. In a recent meta-

analysis of major randomized studies exploring the relationship of RAAS inhibition and worsening renal function, WRF was shown to be more frequent in patients using RAAS compared to placebo. However, in patients with reduced ejection fraction HF, this use was less frequently associated with poor outcomes compared to patients with WRF in the placebo group³. Hence, the occurrence of WRF does not eliminate the survival benefit of RAAS blockade compared to placebo¹⁵. There is therefore compelling evidence to support the prescription of RAAS blockers at the maximum tolerated dose despite moderate renal dysfunction which may occur under treatment.

In contrast to the large body of evidence of the benefits of RAAS blockade in HF with reduced ejection fraction (HFrEF), the evidence of benefit in HF with preserved ejection fraction is subject to continuing debate¹⁶. This review will therefore only address chronic heart failure outpatients with reduced ejection fraction. Of note, acute management is not considered in this review while each minutes count¹⁷.

In this expert panel comprised of heart failure specialists, geriatricians and nephrologists, we review the pathophysiology of renal function worsening and propose targeted therapeutic management algorithms for physicians treating chronic HF outpatients, the latter of which remains a persisting critical concern.

Pathophysiology of Worsening Renal Function in Chronic Heart Failure Patients

Recent reviews have focused in detail on the pathophysiology of renal dysfunction during heart failure¹⁸. In chronic heart failure patients, a number of different mechanisms can induce WRF. Most cases are related to changes in extracellular volume and blood pressure: congestion, hypotension and dehydration are the main drivers of WRF in HF patients. All of these mechanisms are summarized in Figure 1. Importantly, other causes of renal dysfunction should also be systematically investigated, including urinary obstruction.

In normal subjects, renal perfusion remains stable for mean BP as low as 60 mmHg owing to autoregulation. A sufficient pressure gradient within the glomerulus is essential to maintain adequate filtration (Figure 1). This gradient is dependent on glomerular hydrostatic pressure, oncotic pressure and pressure within Bowman's space¹⁹.

Congestion

Congestion is a major factor of WRF in chronic heart failure patients²⁰ and is often an underestimated clinical parameter. In a cohort of 145 patients with mean LVEF of 20% 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 function²¹.

Moreover, in studies using renal venous Doppler to assess renal perfusion patterns in patients with acute heart failure²², renal hemodynamics was clearly shown to improve with decongestion. Conversely, intravascular volume expansion resulted in a significant blunting of renal venous flow causing WRF²³. Owing to increased renal venous pressure, renal interstitial pressure rises above hydrostatic pressure²⁴. This results in tubular collapse with an increase in tubular pressure which, in turn, decreases the net ultrafiltration pressure thereby resulting in decreased renal filtration²⁵.

Finally, in heart failure patients, persistent congestion combined with WRF is significantly associated with adverse outcomes in comparison to WRF without congestion²⁶.

Dehydration/hypovolemia

Dehydration is a common occurrence in heart failure patients. Dehydration is mostly the consequence of excessive diuretic treatment and is more frequently observed in elderly patients with HF (mainly HF with preserved ejection fraction) ²⁷. Dehydration leads to renal hypoperfusion and prerenal renal failure. Pre-renal 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 hypovolemia 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 HF treatments and altered autoregulation in chronic kidney disease (CKD) patients due to structural remodeling of the vascular wall and vascular hyalinization ¹⁹. However, in clinical studies, the link between systolic BP and WRF remains weak ^{2, 20}. Hypotension is nevertheless a major barrier to optimal medical treatment in outpatients with HF ^{9, 10}.

Nephrotoxic drugs

Nephrotoxic drugs are drugs that cause glomerular and/or nephron damage as opposed to reversible hemodynamic effects induced by non-steroidal anti-inflammatory drugs (NSAIDs) and RAAS blockers. The renal toxicity mechanisms of NSAID are multiple and complex (hemodynamic for acute effects, immuno-allergic, 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 hemodynamic 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 patients ^{4, 14, 28}. In most randomized controlled studies, introduction of

RAAS-blockade was associated with a mean 3 ± 4 ml/min/1.73m² 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. This effect is rapidly reversible after treatment suspension.

This 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 HR, 1.0; 95% 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 displayed a significant survival benefit with enalapril therapy (adjusted HR, 0.66; 95% CI, 0.5–0.9; P=0.018). Consequently, while RAAS-blocker can reduce GFR, this reduction is not associated with worse outcome and the benefit of HF treatment remains significant.

Recently, a new “kid on the block” with direct renal effects has appeared in the field of heart failure. The sodium-glucose co-transporter 2 inhibitors reduce the glomerular hyperfiltration present in diabetic patients and reduce heart failure events with a better protection of renal function in HFrEF patients. In the DAPA-HF study, dapagliflozin significantly reduced cardiovascular death and heart failure events without increase in WRF compared to placebo. Further evidence based randomized trials and real-world data are needed to better understand the benefits of this new HF therapy and their impact on renal function³⁰.

Populations at risk of developing WRF

High-risk patients are patients 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. The latter is the consequence of several factors, including the progressive decline in renal function (nephron loss), increased co-morbidities, more advanced heart failure, poly medication with its associated risk of interaction, overuse of inappropriate drugs, and the underutilization of effective treatments^{31,32}.

Table 1: Clinical features differentiating congestion-related WRF from dehydration-related WRF in heart failure patients

	Congestion	Dehydration
Clinical history	Progressive dyspnea, orthopnea, weight gain, edema, 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
Edema	Present in lower limbs	Absent
Diuresis	Oliguria	Oliguria
Signs of heart failure	Jugular turgescence, hepatalgia, pulmonary crackles, pleural effusion, etc.	Absent
Blood pressure / heart rate	Normal or low / increased	Normal or low, orthostatic hypotension / increased
Biological data:		
Plasma	Increased natriuretic peptides compared to “dry weight” baseline value, hemodilution	Hemoconcentration (increased protein concentration and hemoglobin/hematocrit)
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

Assessing Renal Function in Heart Failure Patients

The accurate assessment of renal function is a challenging task in chronic heart failure patients for several reasons.

First, glomerular filtration rate (GFR) estimation equations have all been validated to be used in a steady state setting, which is not always the case in patients with heart failure. In hemodynamically unstable conditions, intra-individual variations of 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 due to the fact that malnutrition and sarcopenia are frequent in this setting. The presence of sarcopenia in HF patients induces an overestimation of GFR. In this regard, serum cystatin C, known to be less dependent on muscle mass than serum creatinine, could represent an appealing alternative³³. In effect, the GFR estimation equation using cystatin C values has been shown to be more robust than the classical creatinine-based 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 HF patients 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 cases of advanced age and/or malnutrition since its measurement results overestimate true renal function. For drug dosing adjustment, many experts advocate specifically using the Cockcroft-Gault formula, which was actually used in drug clinical trials to define the study population. This should be balanced with the fact that “weight”, a particularly fluctuating and confounding variable in patients with HF, is integrated into the formula.

In any event, when a heart failure patient presents with significant renal dysfunction (GFR<45 ml/min), the patient should be considered for referral to a nephrologist for management optimization.

The rapid referral to a nephrologist is furthermore mandatory in instances of i) an increase in creatinine level > 100% of the reference value, ii) a new decrease in eGFR $\leq 20\text{mL}/\text{min}/1.73\text{m}^2$ and iii) persistent hyperkalemia > 5.5mmol/L despite adequate therapeutic management.

Initiation and titration of ACE-I, ARB, ARNI and MRAs

The first introduction of RAAS blockers is critical. Whether this initial introduction is performed in hospital or in the outpatient clinic, the goal is to reach the maximal recommended dose or, if unfeasible, the maximum tolerated dose. Beneficial effects of RAAS blockers are likely dose-dependent³⁴. High doses of RAAS blockers can be prescribed in CKD patients as in the general population, albeit with a closer clinical and biological follow-up. In most cases, WRF should not be a limitation for the titration of beta-blockers. Titration can be performed by various means depending on the patient's history, his/her clinical situation (blood pressure, congestion) and naturally, the patient's 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 one 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 his family should be educated regarding signs of dehydration, hypotension and weight. Information should also be provided as often as possible relative to ideal water and salt intake according to the weather/temperature or physical activity.

As the titration of RAAS blockers occurs concomitantly with the titration of beta-blockers, the sequence in the modification of HF drugs should be anticipated. Usually, the increase in the dosage in 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 demonstrated beneficial effects which result from actions on different pathophysiological pathways. In addition, in the 2016 ESC guidelines,⁷ MRAs initiation follows the ACEi/ARBs and beta-blockers titration.

In patients without clinical signs of congestion, a down-titration of diuretics may favor the titration of RAAS blockers³⁵ and beta-blockers.

The following at-risk situations should prompt a careful clinical follow-up:

- recent hospitalizations with intense diuresis (weight loss > 4 kg),
- other causes of dehydration (gastrointestinal disorders, fever, heat wave),
- elderly > 80 years,
- diabetes,
- prior renal failure (baseline GFR < 60 ml/min/1.73m²).

Facing Worsening Renal Function in a chronic HF outpatient

General Considerations

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

In case of WRF, guidelines from expert task forces have been published by the ESC group (Web addenda) ⁷. These guidelines were based on interpretation from available evidence in different randomized clinical trials and registries. None of the recommended thresholds have been currently assessed in randomized clinical trials. These guidelines can be summarized in 3 general rules:

- An increase in creatinine level after RAAS blocker initiation is frequent and is acceptable up to 50% above baseline value. In the same manner, an increase in potassium to ≤ 5.5 mmol/L is acceptable.
- For increases in creatinine $>50\%$ and below 100% of 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 Figure 2). Apply careful and close follow-up after any strategy change.
- If potassium rises to >5.5 mmol/L or creatinine increases by $>100\%$ baseline or >310 $\mu\text{mol/L}$ or $\text{GFR} < 20 \text{ mL/min/1.73m}^2$, current ACE inhibitors (or ARB or ARNi) and MRA should be stopped and specialist advice from a nephrologist should be sought. In all instances of hyperkalemia >5.5 mmol/L, a second blood sampling should be performed for verification, due to potential confounders such as hemolysis.

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 are to set a pragmatic, simple and systematic management algorithm in various clinical settings for clinicians faced with WRF in a chronic heart failure outpatient.

Urgent Hospitalization Referral

The first practical question to answer is to determine which patients require hospitalization. From our consensus panel, here are the situations where the physician should consider patient referral as soon as

possible to an emergency department, ideally to a hospital with expertise in HF management. These clinical settings are summarized in Table 2.

Table 2. Clinical settings requiring urgent hospitalization

Main clinical settings requiring urgent hospitalization
<ul style="list-style-type: none">• Increase in creatinine > 100% or underlying CKD with acute decrease in eGFR < 20 ml/min/1.73m²
<ul style="list-style-type: none">• Acutely decompensated HF
<ul style="list-style-type: none">• Severe ionic disorders such as hyponatremia <125meq/l, hypokalemia < 3mM or hyperkalemia > 6.0 mM (after verification with a second sample)
<ul style="list-style-type: none">• Severe dehydration with symptomatic hypotension
<ul style="list-style-type: none">• Suspicion of cardiogenic shock
<ul style="list-style-type: none">• Any clinical signs of hemodynamic instability with urinary tract issues (obstruction/ infection)
<ul style="list-style-type: none">• Failure of 48-hour outpatient treatment

Clinical aggravating factors such as daily furosemide (or equivalent) >250 mg/day, issues with adherence and isolation, frailty, 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 settings³⁶. According to our consensus panel, the essential parameters to take into consideration before changing treatment are as follows (Figure 2):

1) **Clinical context:** any concomitant disorder that could alter renal function status (infection, diarrhea, hyperthermia, acute heart failure decompensation, urinary tract pathology), drugs (NSAID introduction) and diet adherence;

2) **Congestion** (Table 1): increase in weight, orthopnea, jugular distension, lower limb edema, increase in natriuretic peptide levels, decrease in Hb/hematocrit, ultrasound parameters showing pulmonary (increased LVEDP) and systemic congestion (raised right atrial pressure)³⁷.

3) **Blood pressure:** symptomatic hypotension, orthostatic hypotension.

4) **Diuretics dose and clinical signs of dehydration**

5) **Nephrotoxic drugs:** NSAID, contrast media, antibiotics, HIV drugs

6) **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 hyperkalemia (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 Figure 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.

Chronic heart failure patients may develop resistance to loop diuretics requiring an increase in dose in order to maintain diuresis. Spreading the diuretic dose in two to three times a day helps prevent this resistance. When a patient develops resistance to a particular loop diuretic, switching to another with higher bioavailability (furosemide to bumetamide or torasemide for example) 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 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, while ambulatory administration of IV loop diuretics has become another option in the 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 since 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/1,73m²) or high 24-hour doses of furosemide (i.e. > 250 mg/d). Hyperkalemia as well as hypokalemia must be investigated and corrected.

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

Dehydration/Hypovolemia

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

Management is incremented according to severity (see Table 2):

- In less severe cases, management must be personalized in this outpatient setting:
 - Down-titrate or discontinue diuretics including that of mineralocorticoid receptor antagonists in most cases,
 - In cases of previous diuretic combination, first suspend thiazide alone,
 - Maintain RAAS blockers at same dose or 50% decrease in doses, maintain beta-blockers,
 - Alleviate low-sodium diet,
 - Blood test within 7 days and new assessment:
 - Improvement: consider pursuing diuretic at same down-titrated dosage; repeated blood test should be performed 48h or 72h later
 - Stability: no change and blood test 48 hours later.
 - Worsening: diuretics and RAAS blockers are discontinued and rehydration increased; blood test the following day; immediate hospitalization is discussed.
- Therapeutic education of the patient and his/her relatives is essential in all cases.

Symptomatic Hypotension

Prescription of all cardiologic treatment without proven outcome benefits in HFrEF (nitrates, calcium-blockers) and non-cardiologic hypotensive drugs (alpha-blockers, antiparkinson drugs, phosphodiesterase inhibitors, etc.) should be reevaluated. 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 diabetic patients. The decrease in RAASi/ARNi/ beta-blockers 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/under-dosing of ACE/ARBs (67.5%/26%) than of beta-blockers (27.9%/17%). As a consequence, down-titration of RAASi rather than beta-blockers may appear appropriate in the context of symptomatic hypotension with WRF unless patients have low heart rate. The magnitude of the down-titration should be personalized to the level of hypotension and WRF as well as patient's characteristics.

Regardless of the change applied to drug prescription, patients with hypotension should be re-assessed. If hypotension is resolved, re-assessment of heart failure drugs should be performed and up-titration should be re-initiated if the patient is not at target doses.

Hyperkalemia

Hyperkalemia, which is a potential life-threatening condition owing to its conduction disturbance properties⁴¹, is an inherent risk associated with RAASi use. In order to achieve the best benefit associated with RAASi use as per demonstrated in clinical trials, it is of utmost importance to adhere to

contraindications related to kidney function and serum potassium⁴². According to these guidelines, potassium levels can be tolerated up to 5.5 mmol/l in a stable chronic HF patient. Furthermore, it should be reminded that MRA introduction is often associated with a significant increase in potassium levels, e.g. approximately 0.5 ± 0.2 mmol/l for 25 mg of spironolactone daily.

In all cases, an appropriate monitoring is warranted. Beyond baseline assessment, creatinine and potassium levels 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 levels or induce WRF. On a routine basis, potassium and serum creatinine should be monitored monthly for the first 3 months, then regularly at 3- to 4-month intervals⁴³.

Once the diagnosis of hyperkalemia is confirmed (i.e. a pseudo-hyperkalemia is ruled out), a “significant” hyperkalemia, associated or not with WRF, should prompt a reappraisal of concomitant drug prescription (e.g. withdrawal of all potassium supplements, e.g., potassium chloride, or salt substitutes, non-steroidal anti-inflammatory drugs or other nephrotoxic drugs). This may also warrant the temporary down-titration or discontinuation of MRAs first. Then, in a second step, reduction or discontinuation of RAASi/ARNi could be considered⁷.

The conjunction of hyperkalemia and WRF should prompt cardio-nephrologic interactions and should target the restauration of renal function (as hyperkalemia may be secondary to the WRF).

The availability of new potential binders (e.g. patiromer or sodium zirconium cyclosilicate) may however offer new opportunities to overcome hyperkalemia. An ongoing trial will determine whether the use of these medications improve CV outcome (DIAMOND trial ClinicalTrials.gov Identifier: NCT03888066). For the time being, potassium binders may be considered when hyperkalemia is the main issue to treat and renal function remains acceptable. They can be useful to stabilize and treat hyperkalemia between 5.5-6 mmol/l allowing maintaining RAASi treatment⁴⁴. However, careful renal function and blood potassium monitoring is mandatory in this setting.

Specificities in the elderly/very elderly

Elderly patients (particularly those >80y) deserve special attention. HF 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 HF and renal dysfunction. In addition, polymedication, which is frequent in this population, further increases the risk of worsening renal function and hyperkalemia through nephrotoxic drug interactions.

In addition, these patients may experience persistent edema while exhibiting hypovolemia during aggressive diuretic treatment, possibly due to delayed vascular refilling.

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

Table 3. Essential rules for RAASi management in elderly patients

Practical Rules in Elderly (≥ 80 years old) Patients
<ul style="list-style-type: none">• eGFR is usually overestimated due to sarcopenia
<ul style="list-style-type: none">• Orthostatic hypotension is frequent and associated with poor outcome. Diuretic dose reduction and/or vasodilator down-titration may be advocated
<ul style="list-style-type: none">• Pay attention to frailty, cognitive disorders and poly medication
<ul style="list-style-type: none">• Monitor congestion closely after diuretic dose increase – Diuretic dosage should be carefully reevaluated after normalization of volemia.

Conclusion

RAAS blockers are a life-saving treatment in HFrEF patients, regardless of worsening renal function. Up-titration to the maximum tolerated dose should be a constant goal. This simple fact is all too often forgotten and 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 a poor assessment of the patient's clinical situation. In the management of chronic HFrEF patients, monitoring of renal function and blood potassium is just as important as the complete clinical assessment of the patient. Each HF patient needs a holistic evaluation of all clinical and paraclinical parameters in order to determine the most beneficial drug combination in terms of individual benefits and risks.

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Figure Legends

Figure 1 Main Factors Influencing Glomerular Filtration Rate in Chronic Heart Failure Patients. RAAS: renin angiotensin aldosterone system; GFR: glomerular filtration rate; NSAI: non steroid anti-inflammatory.

Global Glomerular Filtration Rate (GFR) = nephron number x single nephron GFR

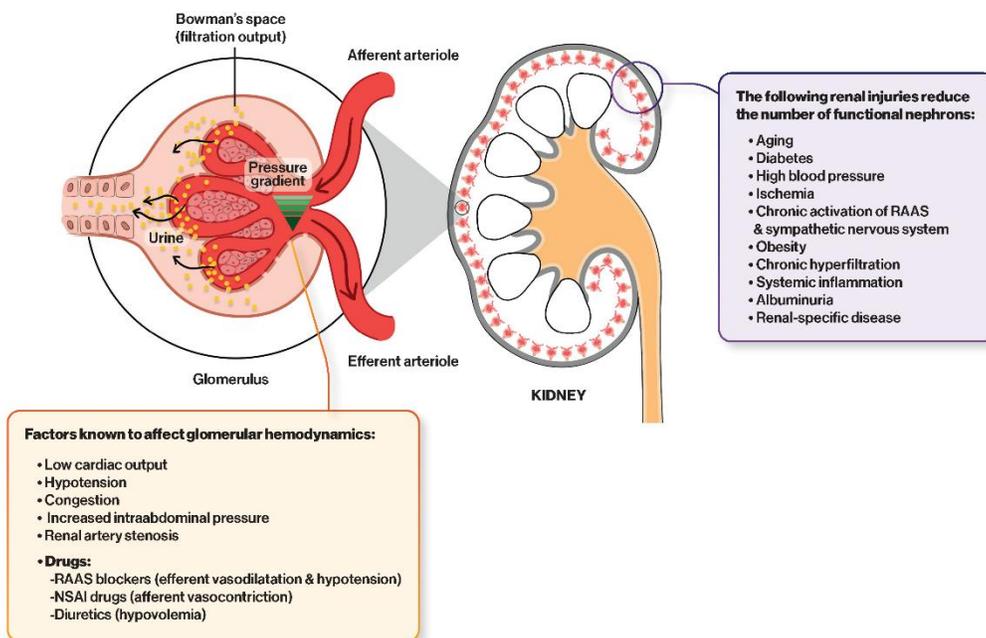
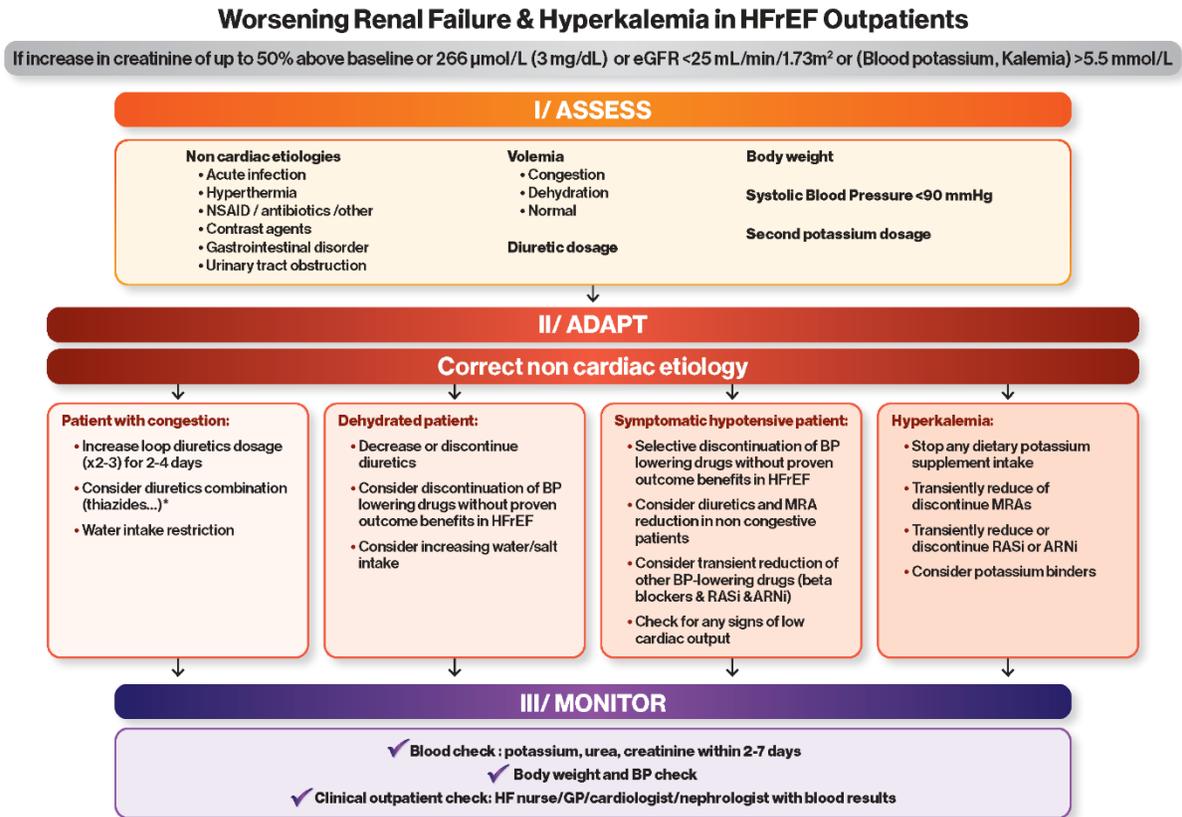


Figure 2. A2M algorithm for the management of HFrEF patients with WRF and/or hyperkalemia. GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; NSAID, non-steroid anti-inflammatory drug; BP, blood pressure; MRA, mineralocorticoid receptor antagonists; RASi, renin angiotensin system inhibitors; ARNI, angiotensin receptor neprilysin inhibitors.



* Preferably in hospital to monitor urinary output enhancement