Optimal RAASi in the patient with CKD/HF: interpreting guidelines through the lens of recent data

Panellist:
Shelley Zieroth,
Canada

Panellist:
Biff F. Palmer,
USA

Panellist:
Maria Soler,
Spain

Moderator:
Smeeta Sinha,
UK

A growing number of patients with the dual burden of chronic kidney disease (CKD) and cardiovascular disease has prompted a close collaboration between nephrologists and cardiologists in recent years. Hyperkalaemia is a common topic of discussion, as both specialties focus on optimizing renin-angiotensin-aldosterone system inhibitors (RAASi) therapy in patients with CKD and heart failure. In advanced stages of CKD, 40 to 50 percent of patients suffer from hyperkalaemia, particularly those with diabetes mellitus and patients on RAASi medication, whereas as many as 40 to 50 percent of patients with severe heart failure on spironolactone therapy also experience hyperkalaemia.

The 2021 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease highlights that patients should, whenever possible, be put on the maximum approved dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Even when these are used in doses that no longer affect blood pressure, the additional anti-proteinuric benefits and renoprotective qualities remain, justifying this recommendation. In addition, proteinuria and the urine albumin-creatinine ratio (uACR) are becoming recognized risk factors for cardiovascular events and heart failure outcomes among cardiologists. The 2021 European Society of Cardiology and 2022 Heart Failure Society of America guidelines stipulate four fundamental management strategies for heart failure with reduced ejection fraction (HFrEF), emphasizing RAAS inhibition as the key component in the treatment of acute and chronic heart failure. Besides ACE inhibitors and angiotensin receptor/neprilysin inhibitors (ARNIs), beta-blockers and mineralocorticoid receptor antagonists (MRAs) are also included in this multimodal treatment.

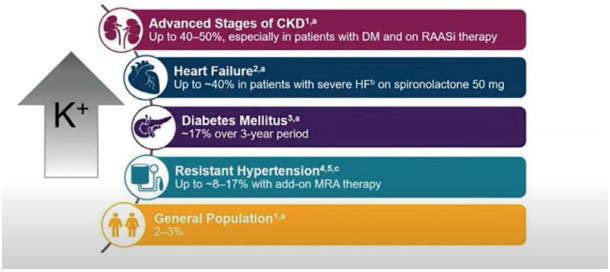


Figure 1.
Cardiorenal patients are at increased risk of hyperkalaemia

From the perspective of nephrology, using maximum doses of RAAS inhibitors amplifies the anti-proteinuric effect even when there is no major change in blood pressure, but it also carries a risk of acute kidney injury. Nevertheless, a slight rise of creatinine which may accompany the initial administration of ACEi or ARBs is less likely to occur at high doses in the absence of a considerable change in blood pressure.

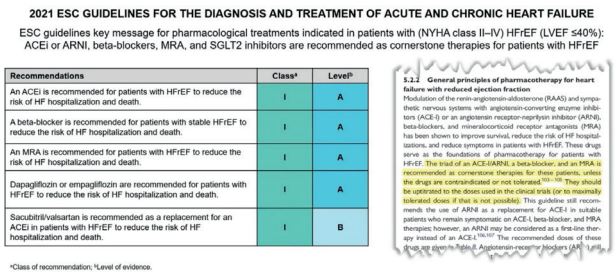
In both CKD and heart failure populations, RAASi therapy is associated with lower mortality and fewer significant adverse cardiac events. The benefit occurs regardless of the target dose, but the protective properties grow with increased dosage, provided that safety monitoring is maintained. On the other hand, down-titration of RAASi therapy is associated with increased mortality in CKD, heart failure, and diabetes, while the highest risk emerges with discontinuation of RAASi therapy, both due to dysregulated blood pressure and hyperkalaemia. In the

event of hyperkalaemia, patients are less likely to be reintroduced to disease-modifying therapy, such as ACEi and ARBs in proteinuric kidney disease or ACEi/ARBs/sacubitril/valsartan/MRA in HFrEF, and it is crucial to explore opportunities to manage hyperkalaemia, such as a low potassium diet, potassium binders, and diuretics.

Approach to RAASi-associated hyperkalaemia

Traditional hyperkalaemia treatment options have their limitations. Diets low in potassium are difficult to adhere to, and restricting potassium-rich foods can lead to constipation and worsen chronic hypertension. The efficacy of diuretics depends on residual renal function. They increase the risk of gout and diabetes and, depending on the diuretic chosen, they may cause volume contraction provoking an azotemic response, cause hypomagnesemia, and raise uric acid levels. Traditional potassium binders such as sodium polystyrene sulfonate have not been tested for their long-term efficacy and they may produce gastric irritation, anorexia, nausea, vomiting, constipation, and occasional diarrhoea. Their hard, gritty texture and disagreeable flavour may reduce their palatability. They also carry a significant risk of hospitalization and death due to serious gastrointestinal adverse effects.

Hyperkalaemia in patients receiving RAASi often prompts the discontinuation or dose-reduction of this therapy, even though it can generally be managed by merely monitoring potassium. European Society of Cardiology Guidelines from 2021 advises that the administration of potassium binders to control chronic or recurrent hyperkalaemia may permit the initiation or up-titration of RAASi if potassium levels are closely monitored. In addition, potassium-lowering therapy should be continued unless an alternative treatable aetiology for hyperkalaemia is identified.



2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HEART FAILURE

ESC guidelines key message for pharmacological treatments indicated in patients with (NYHA class II–IV) HFrEF (LVEF ≤40%): ACEi or ARNI, beta-blockers, MRA, and SGLT2 inhibitors are recommended as cornerstone therapies for patients with HFrEF

Recommendations	Class[a]	Level[b]
An ACEi is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

[a]Class of recommendation; [b]Level of evidence.

5.2.2 General principles of pharmacotherapy for heart failure with reduced ejection fraction

Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor–neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. These drugs serve as the foundations of pharmacotherapy for patients with HFrEF. The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated.[103–105] They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). This guideline still recommends the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I.[106,107] The recommended doses of these drugs are given in Table 8. Angiotensin-receptor blockers (ARB) and

Figure 2.
2021 ESC Guidelines for the diagnosis and treatment of heart failure

The traditional potassium binders, such as sodium polystyrene sulfonate, have rather unpleasant and potentially serious side effects. The novel binders, such as sodium zirconium cyclosilicate (SZC) and patiromer, have proven to be remarkably effective, even for shorter periods of use, intending to keep patients on RAASi. In long-term SZC studies, most patients treated for hyperkalaemia who were on RAASi therapy at baseline maintained the same dose or increased their RAASi dose. In terms of heart failure, data is being obtained regarding the use of SZC and patiromer to assist disease-modifying therapy, particularly MRA.

The PRIORITIZE HF trial results showed no statistically significant difference between SZC and placebo in the various RAASi treatment categories at three months.[1] Nevertheless, there was an increase in MRA up-titration in the SZC group. In addition, the mean serum potassium concentration was quantitatively lower in the SZC group, despite a larger proportion of patients reaching the MRA dosage target. This was well tolerated, with a minimal incidence of adverse events associated with oedema, no indication of an elevated risk of developing HF, and no cases of severe hypokalaemia.

The DIAMOND HF trial was designed to evaluate patiromer with control among patients with HFrEF and a history of hyperkalaemia receiving RAASi and MRA in optimal doses. Patiromer was able to maintain lower serum potassium levels and was associated with a lower incidence of severe hyperkalaemia compared with control. During the open-label run-in phase, the use of patiromer allowed for 85% of participants to be on optimized guideline-directed medical doses of RAASi in this trial.[2]

[1] PRIORITIZE HF was stopped early due to COVID and was under enrolled (underpowered). Results are exploratory.

[2] this data is from the open-label run-in phase in which all patients received patiromer while their RAASi was uptitrated

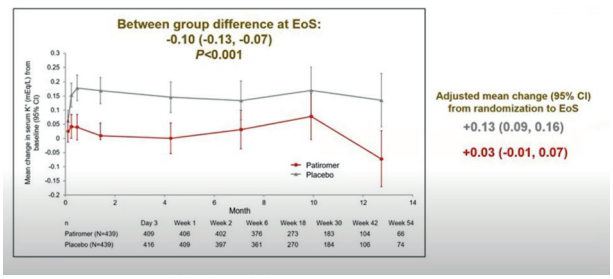


Figure 3.
DIAMOND HF – primary endpoint: Change in serum potassium from baseline

Finally, the REALIZE-K is a prospective, double-blind, placebo-controlled randomized trial enrolling symptomatic HFrEF patients on guideline-directed medical therapy with either hyperkalaemia or at high risk for hyperkalaemia during MRA titration. This ongoing Phase IV trial is evaluating the efficacy and safety of SZC in patients with HFrEF who have been optimally treated with spironolactone. All patients, whether at high risk of hyperkalaemia or with concurrent hyperkalaemia, are administered SZC as needed to facilitate the up-titration of MRA. The primary endpoint is to evaluate the efficacy of SZC compared to placebo in keeping normokalaemia while on spironolactone ≥25 mg daily without hyperkalaemia rescue therapy. Several safety secondary objectives are also potassium-related, such as comparing the SZC and placebo arms for time to the first hyperkalaemia event during the treatment phase and dose reduction or drug cessation due to hyperkalaemia.

Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.

KEY POINTS

1. Based on data from landmark trials, CKD and HF treatment guidelines suggest that RAASi should be initiated and titrated to the highest tolerated dose to improve patient outcomes.

2. Despite the proven benefits of RAASi therapy, hyperkalaemia continues to be a barrier and can result in dose reduction or discontinuation, leading to worse patient outcomes, including an increased mortality risk.

3. Different guidelines discuss managing hyperkalaemia with potassium binders, so that patients may achieve and maintain optimal RAASi therapy.

4. Sodium zirconium cyclosilicate can be used to treat hyperkalaemia while optimizing guideline-recommended RAASi therapy.

5. The ongoing REALIZE-K study is expected to provide more data on the efficacy and safety of SZC in HFrEF patients treated with spironolactone.

Further readings

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