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SPECIAL ARTICLE

Consensus on the management of hyperkalemia in patients with heart failure: Recommendations from the SEC-SEMI☆

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Abstract Use of renin-angiotensin-aldosterone system inhibitors (RAASi) in patients with heart failure (HF) and reduced ejection fraction is associated with functional improvement, an increase in perceived quality of life, a reduction in the probability of cardiovascular death, and a decrease in the number of hospitalizations. Some of these drugs are also efficacious in patients with chronic kidney disease and albuminuria as well as in patients with resistant hypertension. Despite their numerous benefits, RAASi are associated with an increase in incidence of hyperkalemia, especially in patients with concomitant chronic kidney disease. Hyperkalemia is a common electrolyte disorder that is defined as an elevation in plasma concentrations of potassium above 5 mEq/L. It has been related to rehospitalizations, malignant arrhythmias, and an increase in mortality. On the other hand, optimized treatment with RAASi requires progressive dose increases which can in turn entail a greater probability of hyperkalemia. For all of these reasons, it is necessary to establish management and treatment guidelines for these patients. This consensus document arises from this objective. Its recommendations have been developed by a group of ten experts and reviewed by a panel of another ten specialists in the treatment of patients with HF (ten cardiologists and ten internists in total). This document has been endorsed by the Spanish Society of Cardiology (SEC, for its initials in Spanish) and the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish).

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PALABRAS CLAVE
Hiperpotasemia;
Insuficiencia cardíaca;
Enfermedad renal crónica;
Inhibidores del sistema renina-angiotensina-aldosterona

Consenso sobre el manejo de la hiperpotasemia en pacientes con insuficiencia cardíaca: recomendaciones de la SEC-SEMI

Resumen En los pacientes con insuficiencia cardíaca (IC) y fracción de eyección reducida, el uso de los inhibidores del sistema renina-angiotensina-aldosterona (iSRAA) se asocia con una mejoría funcional, incremento de la calidad de vida percibida, reducción de la probabilidad de muerte cardiovascular y disminución del número de hospitalizaciones. Algunos de esos fármacos también resultan eficaces en pacientes con enfermedad renal crónica y albuminuria, así como en pacientes con hipertensión arterial resistente. A pesar de sus numerosos beneficios, los iSRAA se asocian a un incremento de la incidencia de hiperpotasemia, sobre todo en pacientes con insuficiencia renal crónica concomitante. La hiperpotasemia es un trastorno iónico frecuente que se define como la elevación de las concentraciones plasmáticas de potasio por encima de 5 mEq/L, y se ha relacionado con la presencia de rehospitalizaciones, arritmias cardíacas malignas y aumento de la mortalidad. Por otro lado, un tratamiento optimizado con iSRAA requiere de incrementos progresivos de las dosis que pueden suponer a su vez una mayor probabilidad de hiperpotasemia. Por todo ello, es necesario establecer unas directrices para el manejo y tratamiento de estos pacientes. Con este objetivo surge este documento de consenso, cuyas recomendaciones han sido elaboradas por un grupo de 10 expertos y revisado por un panel de otros 10 especialistas en el tratamiento de pacientes con IC (en total 10 cardiólogos y 10 internistas). El documento ha sido avalado por la Sociedad Española de Cardiología (SEC) y la Sociedad Española de Medicina Interna (SEMI).

Introduction

The use of mineralocorticoid receptor antagonists (MRA) along with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), or angiotensin II receptor-neprilysin inhibitors (ARNI) is associated with functional improvement, an increase in perceived quality of life, a reduction in probability of cardiovascular death, and a decrease in the number of hospitalizations for heart failure (HF) in patients with chronic HF and reduced ejection fraction (EF)[1].

On the one hand, ACE inhibitors/ARB can be beneficial in patients with chronic kidney disease (CKD) and albuminuria[2] as well as in patients with resistant hypertension, in whom they reduce events related to target organ involvement, especially in patients with diabetes and chronic kidney injury[3]. However, these drugs are associated with an increase in incidence of hyperkalemia, especially in patients with concomitant CKD[4]. Hyperkalemia has been related to the presence of malignant arrhythmias and an increase in mortality[5]. On the other hand, optimized treatment with these drugs requires a progressive increase in dose which entails greater inhibition of the renin-angiotensin-aldosterone system (RAAS) and thus a greater probability of hyperkalemia[6]. Therefore, new drugs have been added which can correct this progressive increase in potassium without needing to suspend or limit doses of medications which have been proven beneficial.

This document focuses on various perspectives related in particular to moderate hyperkalemia associated with drugs in the context of HF with reduced EF.

Materials and method

A group of 20 experts on the treatment of HF patients was formed (ten cardiologists and ten internists) and coordinated by a clinician from each specialty.

The main topics were selected and distributed among the four working groups, each of which had two members: one cardiologist and one internist. They conducted a literature search on PubMed and in the Cochrane library to select supporting literature. The topics were then brought together and standardized and an action guide was added. The first proposed recommendations were submitted to a review group for evaluation and validation; this group comprised five cardiologists and five internists. Following corrections and comments, the definitive document was created.

Importance of hyperkalemia

Hyperkalemia is a common electrolyte balance disorder that is defined as an elevation in plasma potassium levels above 5 mEq/L. It can be classified according to potassium levels as mild (5–5.4 mEq/L), moderate (5.5–6 mEq/L), or severe (>6 mEq/L)[7]. According to its form of presentation and number of episodes, it can be acute or chronic/recurrent (at least two elevated potassium measurements in a one-year period). The severity of the symptoms it causes does not exclusively depend on potassium levels, but rather also on other factors such as the speed of onset, the patient's comorbidities, the drugs the patient is taking, and the presence of other electrolyte abnormalities[8].

Hyperkalemia is associated with abnormality in the excitable muscle and heart cells, causes conduction disorders and risk of malignant arrhythmias, and is even associated with an increase in mortality[5]. In clinical practice, chronic kidney disease (CKD) and drugs are the factors which most contribute to the onset of hyperkalemia[4], but its prevalence and recurrence increase with the number of comorbidities the patient has. For this reason, it is becoming more and more common among elderly polymedicated patients, especially if they have diabetes, CKD, or HF[9].

In patients with decompensated HF, intensive use of diuretics, activation of the neurohormonal system, and fluctuations in renal function associated with hospitalization make it so there may be a greater presence of hyperkalemia than among patients with chronic HF[10].

Renin-angiotensin-aldosterone system inhibition and treatment suspension due to hyperkalemia

RAAS inhibitors (RAASi)—a wide range of drugs which includes ACE inhibitors, ARB, ARNI, and MRA—currently constitute one of the basic pillars of treatment for various cardiovascular diseases. However, the increase in their use, especially at high doses and in combination with other agents, has led to hyperkalemia becoming a problem, especially in high risk groups such as the elderly and patients with diabetes, HF, or associated CKD[4].

Hyperkalemia is the main reason for not reaching target doses or discontinuing MRA treatment and is the third cause among the other RAASi[11]. RAASi are also underused in patients with CKD who are not on dialysis[12]. These patients are more sensitive to adverse effects such as deterioration in renal function and hyperkalemia. For this reason, management of RAASi in this context is a challenge, and even more so given that there is limited information in this regard.

On the other hand, it is important to take into account that discontinuing RAASi treatment after an episode of HF is associated with greater risk of mortality, readmission, or need for heart transplant[13]. Likewise, the dose of RAASi reached is also relevant. It has been observed that patients who reach <50% of the recommended dose have greater mortality and readmissions due to HF than those in whom maximum doses are able to be titrated[14].

Lastly, hyperkalemia is considered a factor of poor prognosis in HF and of suboptimal RAASi treatment[15]. Therefore, the search for strategies that allow for maintaining RAASi treatment at optimal doses while avoiding adverse effects on renal function and electrolyte balance is important.

Management of hyperkalemia and renin-angiotensin-aldosterone system inhibitors

Recommendations on the management of chronic hyperkalemia in patients in treatment with RAASi vary according to the guidelines consulted, although they are all along similar lines. This document advises following the recommendations proposed by the ESC[1] in its guidelines for the diagnosis and treatment of HF and the recent consensus document by the ESC's Working Group on Cardiovascular Pharmacotherapy[7]. Pursuant to what is stipulated in the latter, adopting measures according to serum potassium levels is advised. These guidelines' objective is to maximize use of RAASi in an attempt to achieve maximum cardiorenal benefits, starting treatments to reduce potassium when levels are greater than 5 mEq/L.

In the case of patients with chronic HF and a medical history of hyperkalemia with or without renal function deterioration, they recommend:

- Discovering the causes that triggered the hyperkalemia; determining its severity, persistence, and reversibility; and recording it on the medical record.
- Identifying patients at risk of developing hyperkalemia again in order to decide whether to retitrate or reintroduce the drug.
- Establishing the target dose, considering the use of potassium-binding drugs, and a schedule for titration and follow-up blood tests, as indicated in the clinical guidelines[1].
- Closely monitoring renal function and electrolytes.

Measures aimed at preventing hyperkalemia include:

- Decreasing potassium intake: low-potassium diet, avoiding mineral supplements, dietary supplements, or multivitamin compounds as well as drugs that contain potassium.
- Increasing potassium elimination: potassium-binding drugs (calcium sulfonate salts, patiromer, sodium zirconium cyclosilicate [ZS-9]).
- Avoiding or optimizing drugs that can deteriorate glomerular filtration and produce hyperkalemia (NSAIDs and a prudent use of potassium-sparing diuretics).
- Achieving the best possible fluid balance in order to avoid renal function deterioration as a trigger of hyperkalemia (appropriate fluid intake according to age, season, etc. and optimization of doses of diuretics).

Table 1 indicates some of the recommendations created by the working group for the identification and management of patients with hyperkalemia and HF (action guide).

Fig. 1 shows the proposed management algorithm.

Conclusions

Hyperkalemia is a common problem in patients with HF that is associated with an increase in morbidity and mortality and is a limitation for the use of first-line drugs recommended in clinical practice guidelines.

The factors most frequently associated with onset of hyperkalemia are: CKD, advanced age, type 2 diabetes mellitus, and previous episodes of hyperkalemia.

On the other hand, there is abundant evidence on the poor functional, clinical, and prognostic progress of patients with an indication for RAASi who cannot take them or reach full doses due to hyperkalemia. The availability of new potassium-binding drugs with a clearly better tolerability and efficacy profile offer the possibility of increasing RAASi prescribing. Therefore, the future outlook is hopeful, with

Table 1 Action guide: recommendations on the identification and management of patients with hyperkalemia and heart failure.

Guide for the identification and management of hyperkalemia in patients with HF
1. **Determine levels of K and eGFR** in all patients with HF.
2. Identify the **type of hyperkalemia**:
- Hyperkalemic emergency.
- Isolated hyperkalemia.
- Recurrent hyperkalemia, mild-moderate, without signs of severity.
3. In all patients with HF, check for a **medical history of hyperkalemia**, determining its etiology and degree of reversibility.
4. The most common **risk factors** are old age, DM, CKD, CVA, neoplasm, medical history of hyperkalemia.
5. Aspects to review to **reduce the risk of hyperkalemia:**
- Decrease intake of K; avoid foods rich in K and K supplements.
- Avoid drugs: NSAIDs, distal diuretics.
- Balance fluid balance; optimize dose of diuretics.
- Evaluate introducing a K-reducing agent.
6. **Indications** with scientific evidence for the **prescription of a RAASi:**
- CKD with albuminuria/proteinuria.
- HT with high cardiovascular risk.
- HF with reduced EF.
7. After indicating a RAASi, establish the **target dose** in order to appropriately titer it.
8. **Therapeutic action** based on K levels:
K = 4–5 mEq/L → Prescribe and/or titer RAASi
K = 5.1–6.0 mEq/L → Evaluate introducing a K-reducing drug and prescribe/titer a RAASi
K > 6.0 mEq/L → Suspend the RAASi and reassess
9. Frequent **periodic follow-up tests** are needed when starting a RAASi:
- First measurement: 1—4 weeks following introduction or titration.
- Repeat at 8–12 weeks. Then every 4 months.
- Closer monitoring of eGFR and K in high-risk patients.
10. If there are criteria for indicating a RAASi and it is not possible to prescribe or appropriately titer one, starting a **potassium-binding drug** is recommended.

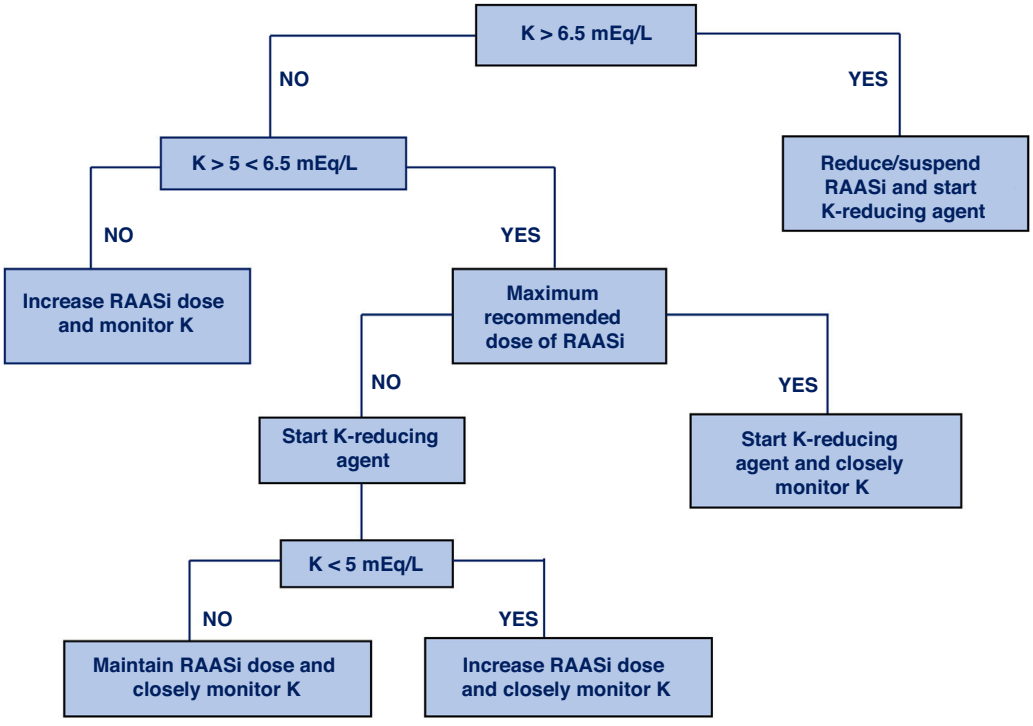

Figure 1 Algorithm for management according to potassium levels.

therapeutic options that allow for addressing such a severe and complex problem as hyperkalemia with the consequent benefits for patients with HF.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.rceng.2020.11.012.

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