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EDITORIAL COMMENT

Potassium and disease-modifying therapy for heart failure with reduced ejection fraction: The beginning of a beautiful friendship?

O potássio e a terapêutica aprimorada para a ICFER: o princípio de uma longa amizade?

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The prognosis-modifying approach in heart failure with reduced ejection fraction (HFrEF) was from the beginning based on vasodilation resulting from blockade of the renin-angiotensin-aldosterone system (RAAS). The CONSENSUS study, and later the SOLVD study, took the first steps in reducing mortality in HRrEF patients.[1,2] In these two studies, the concern over the introduction of an angiotensin converting enzyme inhibitor (ACEI), enalapril, was mainly related to hypotension and worsening of renal function. Cases of hyperkalemia, although clearly more frequent in the enalapril group, were considered minor and were justified by the concomitant use of potassium (K^+) sparing agents, such as spironolactone, or potassium supplementation (CONSENSUS: 7% vs. 4%; SOLVD: 6.4% vs. 2.5%).[1,2] Nevertheless, it is now recommended that potassium levels be monitored when starting an ACEI or changing its dose, since hyperkalemia, when severe, is associated with the risk of malignant arrhythmias.[1]

The RAAS blockade promoted by ACEIs was, however, not sufficient, as it only temporarily suppressed aldosterone production. Reinforcement of this blockade with the addition of a mineralocorticoid receptor antagonist (MRA), spironolactone, was shown in the RALES study to reduce morbidity and mortality effectively and safely in patients with HFrEF who were treated conventionally with ACEIs, diuretics, and digoxin at the time.[3] The incidence of severe hyperkalemia was minimal in both groups of patients, with a mean increase in serum potassium of only 0.3 mmol/L. Gynecomastia was the most relevant adverse effect (10% vs. 1%).[3]

But, despite the RALES study's robust and safe results, real-world evidence has warned of the risk of hyperkalemia resulting from concomitant therapy with an ACEI and MRA. Juurlink et al., analyzing the evolution, before and after the publication of the RALES study, of spironolactone prescriptions in outpatient clinics, hospitalizations for hyperkalemia and hospitalizations for HF, found that in parallel with the increase in spironolactone prescriptions (more than 300%), there was a significant increase in hospitalizations (2.4/1000 to 11/1000) and mortality (0.3/1000 to 2.0/1000) due to hyperkalemia. They did not, however, observe a significant decrease in the hospitalization for HF.[4] This increase in morbidity and mortality associated with hyperkalemia was not disconnected from the concomitant increase in beta-adrenergic blockers prescription seen in this same period. Indeed, the beta-adrenergic blockade, by reducing serum aldosterone, also promotes the occurrence of hyperkalemia. Once again, improved selection of candidates for the pres-

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cription of spironolactone was recommended, alongside strict serum potassium monitoring.[4]

In the paper ''Hyperkalemia as a limiting factor of neurohormonal blockade/modulation in everyday clinical practice'', Cardoso et al. present a real world view.[5] In this retrospective study, 42% of patients with HFrEF followed in an HF clinic had at least one episode of hyperkalemia: 22% moderate (5.6 mEq/L<K^+<6.0 mEq/L) and 3% severe (K^+>6.0 mEq/L). With regard to optimization of the prognosis-modifying therapy, 5% of patients did not achieve optimal doses of RAAS inhibitors and 15% had to discontinue them, totally or partially, due to the occurrence of hyperkalemia.

Hyperkalemia is not a rare condition in patients with HF. Even in the controlled universe of clinical trials in HFrEF, where patients are chosen according to strict criteria and serum potassium monitoring is rigorous when the study drug is introduced, the prevalence of hyperkalemia in the placebo group varies between 2.5% and 12.5%. In the treatment arm, it ranges from 5.7% to 21.7% depending on the patients' characteristics and concomitant medications.[1–4,6] Certain comorbidities, such as chronic kidney disease (CKD) in more advanced stages (eGFR<60 ml/min), diabetes or potassium levels (K^+>5.0 mmol/L) when the RAAS inhibitor drug is introduced, are the main risk factors for the occurrence of hyperkalemia.[6]

The prognosis-modifying therapy for HFrEF is currently based on inhibition of the RAAS, blockade of the sympathetic nervous system, inhibition of neprilysin and, recently, inhibition of the sodium-glucose cotransporter-2 (SGLT2). The interaction of this complex combination therapy is fundamental and has brought about an unprecedented reduction in the morbidity and mortality of HFrEF patients. The benefit of optimized therapy translates into a gain of an additional 2.7 and 8.3 years free of events (cardiovascular death or HF hospitalization) for an 80-year-old and 55-year-old patient, respectively, and an additional 1.4 and 6.3 years of survival for an 80-year-old and a 55-year-old patient, respectively.[7]

The data presented by Cardoso et al. becomes worrying when they mention that only 3% of patients received optimized therapy at the maximum doses and that 20% of patients did not reach this due to the occurrence of hyperkalemia.[5] However, in the data presented, only 4.2% of patients were on sacubitril/valsartan, with no reference to the prevalence of treatment with SGLT2i.[5] This fact is important because the occurrence of hyperkalemia in the PARADIGM-HF study was less frequent in patients on sacubitril/valsartan compared to those on enalapril, both in patients already on MRA and in those who started them during the study. In fact, there was an increased risk of developing hyperkalemia in patients who continued ACEI in the range of 37% to 43%.[8] The same behavior was observed in patients who did not start SGLT2i in the EMPEROR-Reduced study, by showing an increased risk of hyperkalemia events regardless of concomitant background medication: empagliflozin reduced severe hyperkalemia events by 30%.[9] These data suggest the importance of optimizing therapy, with the addition of neprilysin and SGLT2 inhibition, to mitigate the risk of hyperkalemia when MRAs are combined with other RAAS inhibitors in patients with HFrEF.

Being able to initiate, titrate, and mainain prognosis-modifying therapy for HFrEF regardless of concerns over potassium elevation will only be possible when we'll have, as opposed to potassium-sparing agents, a ''potassium-wasting'' drug. For a long time, we have had and used drugs that reduce serum potassium: polystyrene sulfonates, which are cation-exchange resins. Calcium polystyrene sulfonate and sodium polystyrene sulfonate release calcium or sodium respectively in the intestine and reduce the absorption and metabolic availability of potassium. Their effect is unpredictable and usually takes hours to days to occur. But there are frequent and serious unwanted effects, such as constipation or intestinal occlusion, ischemia, necrosis or intestinal perforation as well as hypercalcemia or hypokalemia, strongly limiting the use of these drugs.

In recent years, hope lies in two potassium-binding drugs: patiromer and sodium zirconium cyclosilicate (ZS-9). These have been shown to be effective in rapidly reducing and normalizing, within 48 hours, and preventing recurrence of hyperkalemia in CKD patients on RAAS inhibitor therapy with concomitant diabetes mellitus and/or HF.[10,11] In the PEARL-HF study, patiromer was shown to allow titration of spironolactone (91% vs. 74%, p=0.019) up to the target dose of 50 mg/day in patients with HF and CKD (eGFR<60 ml/L) or with a history of a discontinuation event of an RAAS inhibitor due to hyperkalemia. There was a lower incidence of hyperkalemia (7.3% vs. 24.5%, p=0.015) in the patiromer group, particularly in patients with CKD in whom the incidence of hyperkalemia was 6.7% vs. 38.5% in the placebo group (p=0.041). Adverse events were mainly gastrointestinal (flatulence, diarrhea, constipation, and vomiting; 21 vs. 6%) and hypokalemia (K^+<3.5 mEq/L) occurred only in patients on patiromer (6%, p=0.094).[10] In the HARMONIZE study, ZS-9 achieved normalization of serum potassium in 98% of patients within 48 hours while maintaining it over the four-week follow-up in 90% to 94% of these vs. 46% in the placebo group (p<0.001). Adverse effects were overlapping with hypokalemia occurring only in the ZS-9 treated group (10% to 11%). The concern with the use of this drug in patients with HF, due to its mechanism of action, is related to the occurrence of peripheral edema, with an incidence ranging from 2% to 14% in the highest and most effective doses of ZS-9.[11]

Achieving optimization of HFrEF-prognosis modifying therapy in all patients is conditioned by the occurrence of several adverse events, of which hyperkalemia plays an important role. These new drugs, in particular the ongoing investigation with patiromer, seem to be promising and will allow HFrEF-prognosis modifying therapy and potassium to begin a beautiful friendship side by side.

Conflicts of interest

The author has no conflicts of interest to declare.

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