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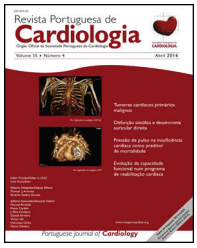

EDITORIAL COMMENT

Maintaining the balance between benefits and risks: The example of hyperkalemia in patients with heart failure

Mantendo o equilíbrio entre os benefícios e os riscos: o exemplo da hipercalemia nos doentes com insuficiência cardíaca

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At the beginning of the 1980s, when I started to care for patients with heart failure (HF), just two classes of drugs were available, diuretics and cardiac glycosides.[1] At that time, my problem was to prevent hypokalemia and related life-threatening arrhythmias.

The first trial showing a clear benefit in mortality reduction for very severe patients with HF was the CONSENSUS 1 trial, published in 1987,[2] and the exciting and extraordinary story of blockade of the neurohormonal system began, revolutionizing the way patients with HF were treated. Over three decades, beta-blockers and renin-angiotensin-aldosterone system inhibitors (RAASIs) – angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid antagonists (MRAs), and, more recently, angiotensin receptor-neprilysin inhibitors (ARNIs) – have been shown to significantly reduce morbidity and mortality in patients with HF and reduced ejection fraction (HFrEF), and are strongly recommended in the current international guidelines.[3,4] The widespread adoption of these drugs in clinical practice has completely changed the attitude of clinicians to electrolyte imbalances: attention moved rapidly from hypokalemia to hyperkalemia.[5] The first alarm signal was sounded in an Ontario population of HF patients treated with spironolactone in addition to ACEIs or ARBs: the use of spironolactone in clinical practice, where potassium and creatinine levels were not as carefully monitored as in clinical trials, was associated with a significant increase in hospital admissions and deaths due to hyperkalemia with or without renal dysfunction.[6]

The increasing number of patients with hyperkalemia, together with the recent introduction of new potassium binders,[7–9] reawakened interest in the epidemiology, prevention and treatment of hyperkalemia, especially in patients with HF, in whom the widespread introduction of RAASIs is raising concerns as to whether these favorable treatments can in fact be offered at appropriate dosages to all patients with HFrEF, given the potential occurrence of hyperkalemia.

The article by Fonseca et al.[10] in this issue of the *Journal* systematically reviews the literature with the aim of assessing the incidence or prevalence of hyperkalemia in patients with HF, the risk factors for developing hyperkalemia, and the impact that discontinuation or dose reduction of RAASIs may have on mortality in these patients. Their review demonstrates that the frequency of hyperkalemia varies widely, from 0% to more than 60%, depending on the setting

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in which data are collected, the type of study (observational versus randomized), and the different populations under study. In general, hyperkalemia was more frequent in observational studies than in randomized clinical trials, in which strict selection criteria excluded by protocol patients at high risk of developing this alarming adverse event. It is worth noting that almost all data refer to patients with HFrEF, whereas very little information is available on HF with preserved ejection fraction (HFpEF). This may be due to the fact that RAASI therapy is not recommended in patients with HFpEF, since no trials have shown a beneficial effect in this clinical condition. However, patients with HFpEF are generally treated with these drugs, even in the absence of evidence-based data, with the aim of improving their symptoms and treating their very frequent comorbidities, such as hypertension or diabetes. More studies should be conducted in patients with HFpEF to assess the rate of occurrence and the prognostic impact of hyperkalemia, which may be no less frequent and no less dangerous than in patients with HFrEF.

With respect to risk factors, the review by Fonseca et al.[10] confirms the role of age, diabetes and chronic kidney disease (CKD) as conditions facilitating the occurrence of hyperkalemia, together with the use of RAASIs, especially MRAs.

Although the authors performed a comprehensive review of all observational and randomized trials analyzing RAASIs and the occurrence of hyperkalemia, the available data are scarce on the impact of discontinuation or dose reduction of these drugs on the outcome of patients with HF. Very recently, a paper using data from the ESC-HFA-EORP Heart Failure Long-Term registry[11] found that discontinuation of RAASIs (ACEIs, ARBs, or MRAs) was consistently associated with all-cause and cardiovascular death, independently of serum potassium at baseline.

In conclusion, careful monitoring of circulating potassium levels and of renal function is necessary in patients with HF receiving RAASI treatment at appropriate dosages to achieve the benefit that these drugs can provide. In order to avoid discontinuation or dosage reduction of RAASI, particular attention should be paid to patients with CKD and/or diabetes, which are very frequent comorbidities and negative prognostic factors in all patients with HF, not only in those with reduced ejection fraction.

More studies should be conducted in real-world settings that assess data collected not only on patients followed by cardiologists, but also on those managed by geriatricians and internists. A more accurate determination of the frequency of hyperkalemia and of the clinical epidemiology of patients in whom this adverse event occurs could be very useful for planning strategies to prevent hyperkalemia and also for better managing this electrolyte imbalance, minimizing the need to discontinue or reduce dosage of RAASIs. These strategies might be also helped by the introduction of the new potassium binders, if their long-term safety and efficacy are definitively demonstrated.

Conflicts of interest

APM has received personal fees from Bayer, Fresenius and Novartis for participation in study committees outside the present work.

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