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EDITORIAL

Mineralocorticoid receptor antagonists (MRAs): more attention required (to prescription)!

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Article Dankowski et al., see p. 1327

Mineralocorticoid receptor antagonists (MRAs; spironolactone or eplerenone) represent an important therapeutic strategy in patients affected by chronic heart failure (HF) with reduced ejection fraction (HFrEF), who remain symptomatic despite treatment with an angiotensin converting enzyme inhibitor (ACEI) and a β-blocker [1]. The benefit of the addition of MRAs to the recommended HF treatment has been demonstrated in a few large multicentre, randomised, placebo-controlled trials that reported a reduction in cardiovascular hospitalisations and mortality in HF patients with mild to severe symptoms and also in patients with symptomatic left ventricular dysfunction after myocardial infarction [2–4].

However, the use of MRAs is related to an increased risk of some serious adverse events, such as hyperkalaemia and worsening of renal function (WRF), which can make cardiologists afraid and reluctant to prescribe this specific treatment.

Data from the European Society of Cardiology Heart Failure Long-Term Registry [5] reported in 2013 that 67% of ambulatory HFrEF patients were on treatment with MRAs and that fewer than one-third of the patients (30.5%) were on the target dosages. About 5% of patients had a real contraindication to the prescription of MRAs. A 5.4% undertreatment rate was observed for MRAs compared with the lower undertreatment rates reported for β-blockers (2.3%) and ACEIs/angiotensin receptor blockers (ARBs) (3.2%). Regarding adverse effects, in the RALES trial [2] the median serum creatinine level increased by 0.05 to 0.10 mg/dL, and the median potassium concentration increased by 0.30 mmol/L in the spironolactone group, with a statistically significant but not clinically relevant difference compared with the placebo group. Thus, more efforts are still needed to implement the prescription of this therapeutic strategy, also considering the potential beneficial effects of MRAs on cardiac function and exercise tolerance.

In this issue of the journal, Dankowski et al. [6] evaluated the determinants of the beneficial effect of MRAs on exercise capacity. This topic has not been extensively studied, and the authors tried to better define the subset of HF patients with a high probability of functional improvement after the introduction of spironolactone. In 2002, Cicoira et al. [7] showed in 106 outpatients with HF a significant improvement in left ventricular volumes and function in patients treated with spironolactone, with the greatest benefits in the group on 50 mg per day; similarly, peak oxygen uptake significantly increased in the group of patients treated with the highest dose of spironolactone (50 mg per day). Dankowski et al. [6] enrolled a sample of 120 stable symptomatic HF patients on treatment with ACEI/ARB and β-blockers, in whom spironolactone 25 mg per day was added to the baseline treatment. Subjects with atrial fibrillation were excluded, and the threshold of left ventricular ejection fraction was moved to < 45% (instead of 35%) to obtain a sufficient sample size; however, an ejection fraction < 35% was present in 55% of the enrolled patients. Improvement of exercise performance was described as an increase in evaluated metabolic equivalents (METs) > 20% at treadmill exercise test using a modified Bruce protocol. Patients exhibiting an increase in exercise capacity after spironolactone showed lower, but not statistically significant, baseline exercise time and METs (absolute and a percentage of the predicted value) compared to subjects who did not improve their functional limitation; moreover, patients performing better after spironolactone had lower baseline B-type natriuretic peptide (BNP) levels. Even if atypical, this paradoxical finding might be related to the presence of more obese patients in the first group (body mass index: 29.3 ± 5.2 kg/m^2 vs. 28.0 ± 4.0 kg/m^2; p = 0.15). As the main finding, the authors reported that the independent determinants of increase in exercise capacity after six months of spironolactone use were the presence of diabetes, baseline BNP, and renal function, expressed as Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration

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rate (eGFR). Specifically, at logistic regression analysis, baseline eGFR improved the model based on diabetes mellitus (C statistic 0.75 vs. 0.64; p = 0.004), and the addition of baseline BNP improved the model based on diabetes and eGFR (C statistic 0.78 vs. 0.75; p = 0.01). Diabetes and baseline BNP were also independent predictors of symptomatic treatment benefit. These results underline that MRAs (spironolactone in this setting) might be responsible for a greater clinical benefit in those patients (diabetics and patients with mild to moderate renal dysfunction — mean eGFR 68 mL/min/1.73 m^2), who are potentially at increased risk of adverse side effects, such as WRF and hyperkalaemia.

According to these results, post-hoc analyses [8, 9] of two large randomised trials, EPHESUS [3] and RALES [2], highlighted the benefits of MRAs, respectively in HF diabetic patients and in HF subjects with renal impairment. O'Keefe et al. [8] analysed the effects of eplerenone compared to placebo in 1483 diabetic patients with post-myocardial infarction systolic dysfunction and HF signs. The authors reported a greater reduction of the *absolute* risk of cardiovascular mortality or hospitalisation in diabetic patients compared to non-diabetics (5.1% vs. 3%). A post-hoc analysis of the RALES trial [9], investigating the influence of baseline renal function and WRF on the efficacy of spironolactone, confirmed that the presence of baseline chronic kidney disease is associated with higher mortality. However, the authors reported that spironolactone maintains its therapeutic efficacy among patients with moderate impairment of renal function.

In particular, in comparison to subjects with a baseline eGFR > 60 mL/min/1.73 m^2, patients with lower eGFR showed comparable *relative* risk reductions in all-cause death and in the combined endpoint of death or HF hospitalisations, but demonstrated a greater *absolute* risk reduction of the same endpoints. Moreover, WRF was not associated with an increased risk of death in the spironolactone group.

The findings of Dankowski et al. [6] are in line with the greater beneficial effect of MRAs in patients with baseline comorbidities such as diabetes and chronic kidney disease. Moreover, the authors also showed that, among different echocardiographic parameters, the augmentation of global longitudinal strain was the only variable significantly associated with a more pronounced improvement of exercise intolerance, and they suggested that global longitudinal strain might be more appropriate than left ventricular ejection fraction to monitor the improvements in left ventricular function under treatment. A better understanding of these interactions will increase our capability to assess the net clinical benefit of available HF treatments aiming to improve clinical outcomes in the long-term.

Although risks of MRA use, including hyperkalaemia and WRF in patients with already impaired renal function and WRF in diabetics need to be continuously addressed and considered, the study of Dankowski et al. [6], together with the previous reported findings, promotes and implements the prescription and use of MRAs in HFrEF patients in order to improve the quality of life and long-term prognosis of our patients.

Conflict of interest: *none declared*

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