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Commentary

Renin-angiotensin-aldosterone inhibition in chronic heart failure: From theory into practice

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Heart failure (HF) is an extremely relevant chronic disease impacting on quality of life and prognosis. Furthermore, the increasing prevalence of HF leads to a huge number of admissions and entails an important use of resources and healthcare costs [1]. For these reasons, the optimization of its management is crucial, including early diagnosis, pharmacological treatment, cardiac devices, HF community programmes, etc.

Regarding pharmacological management, for years neurohormonal blockade has been the basis of medical treatment for HF with reduced left ventricular ejection fraction (LVEF), to which the multifactorial effect of iSGLT2 has been added more recently. The recent Heart Failure Guidelines of the European Society of Cardiology (ESC) [2] recommend treating patients with HF and reduced ejection fraction with the four main pharmacological groups that have been shown to reduce mortality. However, reaching optimal doses of the 4 drugs as soon as possible can become a challenge due to HF patients frequently presenting with arterial hypotension, chronic kidney disease, or hyperkalaemia, among others.

In this context, in this issue of the European Journal of Internal Medicine, Perrone-Filardi et al. have published an elegant review of the scientific evidence supporting the benefit of Renin-Angiotensin-Aldosterone System (RAAS) blockade, focusing on the role of Angiotensin Receptor-Neprilysin Inhibitor (ARNI), to finally present the Italian Society of Cardiology position on the use of ARNI [3]. They begin by reviewing the evidence for the benefit of RAAS inhibition in the HF setting across the LVEF spectrum. In HFrEF, pivotal studies of ACE inhibitors (ACEi) and mineralcorticoid receptor antagonists (MRA) from the past century showed a benefit by decreasing all-cause mortality and readmission for HF compared to placebo [4].

Subsequently, the authors review the evidence about the benefit of ARNI in HF. The PARADIGM-HF study [5], carried out in 8842 patients with chronic HFrEF, demonstrated a 20% decrease in the combined endpoint of cardiovascular (CV) mortality and hospitalization for HF, compared with enalapril. A significant benefit was also demonstrated in each endpoint independently. It should be noted that a 22% reduction in sudden death and 16% in all-cause mortality was also observed. Regarding acute HF, two studies have evaluated the initiation of ARNI during hospitalization for acute decompensated heart failure [6,7]. From these studies we know that ARNI can be safely started during the admission also in de novo HF, decreasing NTproBNP earlier and achieving higher doses of this drug after discharge. Beyond HF, surprisingly, the PARADISE-MI [8] study did not show an improvement with ARNI compared to ramipril in CV and HF mortality in patients with acute myocardial infarction and LVEF <40%. Therefore, we need more studies on the benefits of ARNI in stage B heart failure. The authors review the effects of ARNI on ventricular remodeling. The PROVE-HF study [9] showed the correlation between the decrease in NTproBNP and the reduction in LV volumes, as well as the improvement in LVEF. These differences were demonstrated at 6 months after the ARNI initiation and continued through the 12-month follow-up. The PRIME study [10], in this case a randomized study, showed a benefit of ARNI vs valsartan also in reducing mitral regurgitation quantified by effective regurgitant orifice (ERO).

The evidence in HFpEF is much lower at the moment. The PARAGON-HF [11] clinical trial compared ARNI vs valsartan in 4,822 patients with chronic HF and LVEF >45%. In this case, there were no differences in the primary endpoint (CV mortality or hospitalization for HF), although it opened the door to continue investigating subgroups in which there could be benefit, such as women or LVEF <57%.

To conclude the review of ARNI, the authors address the indications for ARNI in the main clinical practice guidelines. The 2016 American HF

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guidelines [12] recommend ARNI in patients with HFrEF, both in those undergoing treatment with RAASi and in those who were naïve to treatment. In this same group of patients, the recent HF ESC guidelines [2] recommend ACEi and give a grade I recommendation to substitute ACEi for ARNI. Given the scant evidence in patients with slightly reduced LVEF, the guidelines only include a grade IIb recommendation, highlighting the lack of consensus in this group of patients.

Finally, Perrone-Filardi et al. present the position of the Italian Society of Cardiology based on the evidence and provide an algorithm to facilitate the management of ARNI in patients with HF. It is a very useful document where the evidence available to date is applied, although the robust recommendation of RAASi over iSGLT2 has caught our attention. They conclude that RAASi should be recommended before iSGLT2 given that the evidence for this pharmacological group is derived from patients who were receiving treatment with RAASi (including sacubitril-valsartan) and B-blockers. This leads us to the question, should we titrate only strictly according to the chronological order of clinical trials?

Our opinion is that titration should be driven by the clinical profile of the HF patient. This fact is supported by the horizontal algorithms of the HF guidelines of the American Society of Cardiology [13], the Canadian Society of Cardiology [14] and the European Society of Cardiology [2]. These recommendations represent an advance over previous clinical practice guidelines, where a "vertical" titration algorithm required the time factor to see the patient's evolution. It is true that in pivotal studies of iSGLT-2 in HF, as DAPA-HF [15], patients were already under high rates of neuro-hormonal treatment (96% with beta-blockers, 71.5% with MRA and 95% with RAASi). However, this can also be applied to ARNI since PARADIGM-HF [5] patients were receiving treatment with beta-blockers (93%) and MRA (54%). However, there are many scenarios where ARNI should be started before beta-blockers or MRA. On the other hand, ARNI was safe also in the novo patients, since PIONEER-HF [6] and TRANSITION [7] included 34% and 29% de novo patients, respectively.

We have extensive clinical experience and scientific evidence in performing horizontal titration without a rigid starting order of drugs. In pivotal clinical trials of beta-blockers, ACEi and MRA drugs [16], the clinical benefit was observed in all patients (whether or not they were receiving previous neuro-hormonal blockade). More recently, a sub-analysis of PARADIGM-HF [17] observed a decrease in primary end-point regardless of the MRA treatment (p-interaction = 0.104) and beta-blocker dose achieved (p-interaction = 0.973). Regarding iSGLT2, in a sub-analysis of the EMPEROR-Reduced trial [18], the benefit of iSGLT2 was also observed regardless of the treatment with ARNI. Thus, in our opinion, we should not recommend a rigid titration algorithm giving priority to some drugs over the others, but prioritize the medical treatment optimization according to the clinical characteristics of the patient (mainly heart rate, blood pressure, kidney disease and atrial fibrillation) [19].

We agree with the authors about the indication of ARNI being limited in patients with SBP <100 mmHg and eGFR <30 ml/min/m^2 so it is very important to adjust the non-modifying drugs of the disease, such as diuretics and calcium channels antagonists. After the TITRATION study [20], we know that a more conservative titration strategy (in this case within the 6 weeks after the discharge) achieved greater optimization in de novo HF, in patients with SBP <110 mmHg, and in those patients who were not receiving RAASi or who received them at low doses. We can hypothesize that a gentle titration strategy in those patients with a more complicated hemodynamic profile (lower BP, naive for RAASi), will allow for optimal doses of ARNI to be achieved more frequently. Regarding chronic kidney disease it is known that ARNI inhibits neprilisin (increasing natriuretic peptides) leading to a direct afferent arteriole vasodilatation, increasing the diuretic effect and attenuating the fall of eGFR observed in patients with HF. This renal benefit was shown in PARADIGM-HF [5] in which ARNI was associated with lower renal impairment and lower incidence of severe hyperkalaemia. Even in HFpEF ARNI showed lower worsening renal function in PARAGON-HF [11].

In summary, in HFrEF setting, there is an exponential increase in prognosis after combining treatment with ARNI, beta-blockers, MRA, and SGLT2i [21]. The goal should be to achieve quadruple therapy, but it is difficult to apply a rigid algorithm to achieve it. Taking into account the clinical profile, we will be able to find the best pharmacological combination to improve the prognosis of our patients with HF. We want to thank Perrone-Filardi et al. for this elegant review of the knowledge about the use of ARNI in all the spectrum of HF and also for sharing the considerations and recommendations of the Italian Society of Cardiology.

Declaration of Competing Interest

PM has received fees as a speaker and/or consultant from Novartis, Rovi, Boehringer and AstraZeneca.

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