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MRA indication and underuse in high-risk post myocardial infarction patients

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This editorial refers to the paper by Schou M et al. “Sacubitril/valsartan compared to ramipril in high-risk post myocardial infarction patients stratified according to use of mineralocorticoid receptor antagonists: Insight from PARADISE MI trial”¹ published in the *European Journal of Heart Failure*.

The mineralocorticoid receptor antagonist (MRA) eplerenone has been shown to improve the prognosis of patients who had a myocardial infarction (MI) complicated with symptomatic left ventricular systolic dysfunction (LVSD) on top of angiotensin converting enzyme inhibitors (ACEi) in the landmark EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial.² As consequence, the use of eplerenone in this setting is recommended by international guidelines.^{3,4}

Since the publication of EPHEBUS in 2001, the treatment of patients with MI changed significantly with the broad implementation of revascularization, and the addition of novel anti-thrombotic agents, lipid-lowering drugs, and revascularization techniques, resulting in lower rates of recurrent ischemic events and mortality.^{5,6} Therefore, improving outcomes in this population on top of contemporary treatment is increasingly more challenging.⁷ Still, the residual risk after a complicated MI is high and novel strategies are yet needed. In this regard, the PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) trial tested the efficacy and safety of sacubitril/valsartan vs ramipril in 5661 patients who had an MI (within 7 days) with LVSD. Compared with the ACEi ramipril, sacubitril/valsartan did not reduce the independently clinical event classification (CEC) adjudicated primary composite outcome of cardiovascular mortality or incident HF (hazard ratio, HR 0.90, 95%CI 0.78-1.04, p =0.17), nor all-cause mortality (HR 0.88, 95%CI 0.73-1.05, p =0.16).⁸ However, investigator reported primary outcome events were reduced with sacubitril/valsartan vs ramipril (HR 0.85, 95%CI 0.75-0.96, p =0.01), as well as total (first and recurrent) HF events (rate ratio, RR 0.79, 95%CI 0.65-0.97, P =0.02).⁹ These investigator reported and total event observations do not modify the interpretation of the original hypothesis testing, but suggest that sacubitril/valsartan may have a role in patients with MI who develop symptomatic heart failure with reduced ejection fraction (HFrEF). This hypothesis is well supported by the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) trial, which showed superiority of sacubitril/valsartan over enalapril in symptomatic chronic HFrEF.¹⁰

In this issue of the *Journal*, Schou M et al. add relevant information to the literature by assessing the efficacy and safety of sacubitril/valsartan vs ramipril according to MRA therapy in the PARADISE-MI trial.¹ It is important to highlight that, despite being a guideline

recommended therapy for patients who had an MI complicated with LVSD, in the global PARADISE-MI trial, only 41% of the patients were using MRAs at baseline (in contrast with 85% using beta-blockers and 95% using statins).⁸ The potential reasons for MRA underprescription have been detailed elsewhere,¹¹ and have been consistently reported in real-world cohorts.⁴ In the PARADISE-MI trial, patients were randomized to sacubitril/valsartan or ramipril, and MRAs use was left at the discretion of the treating physician. Hence, patients using MRAs had lower LV ejection fraction, more signs of congestion, and worse Killip class, suggesting that doctors prescribed MRAs to “sicker” patients. Therefore, the potential confounders attenuated the association between MRA use and adverse outcomes after statistical adjustment. Still, from a clinical standpoint the paper by Schou M et al. suggests that adding sacubitril/valsartan to MRA was safe and not associated with more symptomatic hypotension or hyperkalemia compared to ramipril on top of an MRA. Furthermore, background MRA therapy did not modify the effect of sacubitril/valsartan vs ramipril on the CEC adjudicated primary outcome or investigator reported outcomes (treatment-by-MRA interaction P-values >0.1 for all reported outcomes).

Knowing the timing of MRA initiation would have been of great value for the interpretation of the findings, as patients taking MRAs for a long time may have a different tolerance to sacubitril/valsartan compared to patients initiating sacubitril/valsartan and MRA concomitantly. Unfortunately, the timing of MRA initiation was not available in PARADISE-MI. Furthermore, based on the EPHEBUS trial, eplerenone should be the MRA of choice in post-MI patients with LVSD or HF;¹² however, the authors could not differentiate between spironolactone and eplerenone use, and did not have data on MRA doses which could also influence the efficacy and safety of both MRAs and sacubitril/valsartan. Additionally, to effectively test whether a new therapy (such as sacubitril/valsartan in MI patients with LVSD) adds benefit on top of guideline-directed medical therapy (GDMT), patients should be treated with GDMT before randomization, and this would include an MRA in most (unless contra-indicated) patients entering PARADISE-MI.

In conclusion, this report from the global PARADISE-MI trial reinforces that MRA are underused in contemporary patients with a clear indication for MRA therapy.¹ Based on the best available evidence, it is important to stress out that eplerenone is recommended by international guidelines for the treatment of patients with MI and LVSD or HF, whereas sacubitril/valsartan is not.³ Still, the addition of sacubitril/valsartan on top of MRA therapy is likely safe and does not seem to have major influence on the clinical effect of sacubitril/valsartan. This is relevant to inform clinical practice, when doctors, based on their clinical judgement, consider adding sacubitril/valsartan to a MRA in patients who had a MI complicated with HFrEF.

Disclosures

None.

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