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Sacubitril-Valsartan, a New Opportunity for Heart Failure with Recovered Ejection Fraction?

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Nowadays, heart failure with reduced ejection fraction (HFrEF) continues to have a poor prognosis. Lupón et al. [1] demonstrated that 1 of 4 ambulatory HF patients with HFrEF treated contemporarily showed "recovery" of systolic function at 1 year and a significantly better mortality and morbidity compared to HFrEF patients.

However, the predictors of recovery do not seem to be clearly established. Agra-Bermejo et al. [2] showed that treatment with ACE inhibitors and beta-blockers was an independent predictor of LVEF recovery.

The effects of sacubitril-valsartan on LV remodeling have been uncertain.

In the PROVE trial analyses of changes in cardiac remodeling indices demonstrated a significant increase in LVEF and corresponding reduction in LV volumes as early as 6 months; and such changes continued at 12 months [3]. Compared with baseline, the 6- and 12-month least-square mean improvements in LVEF were 5.2% (95% CI 4.8–5.6) and 9.4% (95% CI 8.8–9.9), respectively ($p < 0.001$ for both); 75% of the study participants had an LVEF increase of 4.9% or greater and 25% experienced an LVEF increase of 13.4% or greater at 12 months. The greater benefits were observed in those patients with new-onset HF or those not taking an ACEI or ARB at baseline [3].

The study by Díez-Villanueva et al. [4] adds to the knowledge base regarding associations between ARNI therapy and cardiac remodeling. This study included 249 outpatients with HF and reduced LVEF who started sacubitril-valsartan between October 2016 and March 2017. After a mean follow-up of 7 ± 0.1 months, 24.8% of the patients had LVEF >35%. At the end of follow-up, the mean LVEF in the recovery group was 41.9 ± 8.1% (vs. 26.3 ± 4.7%, $p < 0.001$), with an improvement compared with the initial LVEF of 14.6 ± 10.8% (vs. 0.8 ± 4.5%, $p < 0.0001$). In addition, 85% of these patients experienced a LVEF improvement >5%. These findings were associated with lower visits to the emergency department and/or hospitalizations for HF.

In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality in Heart Failure (PARADIGM-HF) study, long-term therapy with sacubitril-valsartan (a combination angiotensin receptor/neprilysin inhibitor [ARNI]) lowered the rates of cardiovascular death or HF hospitalization compared with enalapril. Other outcomes, such as mortality and quality of life, were also favorably affected by the ARNI therapy [5].

The results of Díez-Villanueva et al. [4] suggest that the reverse myocardial remodeling benefit of sacubitril-valsartan happens in the early beginning of the treatment.

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In addition, the study demonstrated that not carrying an ICD or cardiac resynchronization therapy predicted LVEF recovery. These results are similar to those published by Agra-Bermejo et al. [2]. These data may be important before planning device implantation, and require further research to better stratify those HF-recovered patients that do not necessitate an implantable cardioverter defibrillator.

Nowadays, LVEF may be considered to be a guide-element for therapy optimization and follow-up in the same way that was proposed for natriuretic peptides. Given that HF with recovered fraction is a better prognosis entity compared to HFrEF and that the benefits of SV are observed in the first months of treatment, it should be started early in all patients with reduced LVEF in order to improve their prognosis as soon as possible.

Disclosure Statement

The authors have no conflicts of interest to declare.

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