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Editorial

Sacubitril/valsartan in HFrEF – Should the aces up our sleeves be played earlier?

With a total aged-dependent prevalence of ~1–2% and 5-year-survival rate of only approximately 40–50% heart failure with reduced ejection fraction (HFrEF) still represents a major contributor to mortality in western countries and represents an entity deadlier than some types of cancer [1–3].

The 2015 approval of the angiotensin-receptor/neprilysin-inhibitor (ARNi) sacubitril/valsartan had important impact on management of HFrEF patients and represented a milestone in heart failure (HF) treatment. The "Prospective Comparison of Angiotensin Receptor- Neprilysin Inhibitor with Angiotensin- Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure" trial (PARADIGM-HF) investigated effects of sacubitril/valsartan in 8442 patients and was terminated early as it demonstrated a significant reduction in death from cardiovascular causes or hospitalization for HF over the lead substance enalapril [4]. Specifically, ARNi therapy reduced sudden death (HR 0.80, ARNi vs. enalapril, 95% CI 0.68–0.94, P = 0.008) and death due to aggravating heart failure (HR 0.79, ARNi vs. enalapril, 95% CI 0.64–0.98, P = 0.034) [5]. Subsequently, based on this study, HF guidelines were modified to recommending sacubitril/valsartan in HFrEF patients remaining symptomatic in functional class II-IV despite the use of angiotensin-converting-enzyme (ACE) inhibitors [6]. Current HF guidelines were reluctant to recommend ARNi treatment in functional class II-IV as a first line therapy despite superiority of ARNi in comparison the ACE inhibitors. Recent evidence from the "Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode" (PIONEER-HF) trial shows similar efficacy of ARNi treatment in patients with acute decompensation [7]. In this study 881 patients with HFrEF were randomized to sacubitril/valsartan or enalapril with a view to the primary endpoint of time-averaged proportional change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration during short term follow-up. ARNi was more effective than enalapril with respect to the primary endpoint. There were no differences with respect to the secondary endpoint of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema. Recent "Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF" (PARAGON-HF) trial compared ARNi and valsartan therapy in heart failure with preserved ejection fraction (HFpEF) [8]. Unfortunately PARAGON-HF failed to show significant reduction in total hospitalizations for heart failure and death for cardiovascular causes (RR 0.87, ARNi vs. valsartan, 95% CI 0.75–1.01, P = 0.06) in patients with HF and ejection fraction ≥45%. In conclusion, ARNi has not been able to reproduce its course-setting results in HFrEF for HFpEF.

In this issue of the Journal Bayard et al. describe interesting – and very timely - observations from a single-center cohort of 52 patients (n = 41 final population due to active ingredient intolerance) who received treatment with ARNi after rehospitalization on account of HFrEF (≤40%) [9]. Patients were NYHA class II-IV at baseline and had a mean LVEF of 33 ± 5% in line with the label of sacubitril/valsartan. Lack of previous ACE- or AT1-inhibitor therapy was no exclusion criterion. ARNi therapy showed significant improvement concerning various echocardiographic parameters including LVEF (33 ± 5% vs. 36 ± 6%, P < 0.0001). While lack of control group and randomization are the biggest shortcomings of the paper, these observations are in line with previous data and may be used to support an earlier use of ARNi.

As a potential underlying mechanism of action, the combination of sacubitril and valsartan increases renal blood flow, glomerular filtration rate, natriuresis and diuresis while it decreases aldosterone secretion, vasoconstriction and active vasodilatation. In summary leading to an overall volume reduction and accordingly, beneficial reduction in left ventricular preload. ARNi may therefore facilitate reverse cardiac remodeling [4,10–15]. As an effective heart failure therapy, ARNi also seems to have antiarrhythmic effects showing reduced incidence of ventricular arrhtyhmias [16]. For example, de Diego et al. demonstrated that therapy with ARNi led to a significant reduction of ventricular arrhythmias in patients with implantable cardioverter defibrillator and HFrEF compared to therapy with RAAS inhibitors [17]. Since arrhythmogenesis and contractile dysfunction are highly associated, improvement of filling pressures and reversing volume overload, as shown by Bayard *et al.*, may indirectly affect arrhythmia incidence.

The present paper by Bayard et al. reports data obtained prospectively from an observational cohort in a sequential design. Based on an improvement of several echocardiographic parameters the authors emphasize that ARNi reduces myocardial remodeling – in terms of "echo response" (defined as an absolute improvement in left ventricular ejection fraction [LVEF] ≥ 5%) - in patients suffering from HFrEF. Interestingly enough, the authors found no impact on diastolic parameters. These results may offer echocardiographic correlate and explanations for PARAGON-HF results and give space to future studies on the effect of sacubitril/valsartan in patients suffering from HFpEF.

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Although PARADIGM-HF showed fascinating results with regard to patient outcome and data indicate significantly reduced hospitalization related costs [18], sacubitril/valsartan still seems to be used reluctantly and inconsistently too often. Current guidelines provide an indication for ARNi therapy if patients remain symptomatic despite optimal "conventional" therapy. As knowledge about ARNi grows it will be important not to miss the point where an early onset of ARNi therapy should become by no means uncommon.

Disclosure

Nothing to declare.

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