Is There Room for Sacubitril-Valsartan in the Treatment of Advanced Heart Failure?

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PARADIGM-HF, published in 2014, was a landmark in the modern pharmacological treatment of heart failure (HF).[1] After several years and numerous clinical trials with disappointing results,[2-5] a new class of drugs was able to produce concrete results in clinically relevant outcomes. In this pivotal study,[1] sacubitril-valsartan, a molecule consisting of a neprilysin inhibitor and an angiotensin-receptor blocker (ARB), drastically reduced hospitalizations for HF, cardiovascular mortality, and overall mortality. The study included more than 8,000 outpatients, mostly New York Heart Association (NYHA) class II or III. Because of its differential mechanism, aimed at amplifying the natriuretic response and the effect of other vasoactive molecules, sacubitril-valsartan could induce pronounced vasodilation, natriuresis and inhibition of cystic fibrosis. These clinical benefits could potentially be extended to the whole spectrum of HF, including more advanced stages of the disease.

Although national and international guidelines have recommended the use of sacubitril-valsartan for HF patients with reduced ejection fraction (HFrEF) and NYHA class ≥II, it is worth mentioning that <1% of patients had NYHA class IV symptoms at randomization in PRADIGM-HF. In addition, only patients who had received and tolerated a single-blind treatment with a stable dose of ARB or angiotensin-converting-enzyme (ACE) inhibitor (run-in periods) and had a systolic blood pressure > 100 mmHg at screening were enrolled. Nearly 20% of patients screened for the trial did not complete the two run-in periods for presenting, among others, low blood pressure and low glomerular filtration rate, both characteristics of advanced HF. Similarly, the PIONEER-HF trial, that tested sacubitril-valsartan in patients with acute congestive HF, also included few patients with NYHA class IV.[6]

Due to the lack of evidence on the clinical benefits of sacubitril-valsartan in patients with chronic HFrEF and severe symptoms, the LIFE trial[7] was proposed, to test the hypothesis that this therapeutic approach would improve the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as compared with valsartan alone in patients with advanced HFrEF and NYHA functional class IV.[7] The LIFE study was a randomized, double-blind clinical trial with 335 patients with advanced HF, initiated in March 2017 and interrupted due to the COVID-19 pandemic. Patients were randomized to receive sacubitril-valsartan (target dose 200 mg twice daily) or valsartan (target dose 160 mg twice daily), in addition to the standard therapy for HF. The primary endpoint was the proportional change from baseline in the area under the curve (AUC) for NT-proBNP levels measured over 24 weeks of therapy. From patients included in the analysis, 245 were men (73%); men age was 59.4 (±13.5) years; 72 (18%) could not tolerate sacubitril-valsartan 100 mg/day during the run-in period, and 49 (29%) discontinued the drug during the study period. Median NT-proBNP AUC was 1.19 (IQR, 0.91-1.64) in the valsartan treatment arm (n = 168), whereas the AUC for the sacubitril/valsartan treatment arm (n = 167) was 1.08 (IQR, 0.75-1.60). The estimated proportional change in the NT-proBNP AUC was 0.95 (95% CI 0.84-1.08; p = 0.45). Compared with valsartan, treatment with sacubitril-valsartan did not improve the clinical outcome of number of days alive out of hospital and free from HF events (103.2 vs. 111.2 days; p = 0.45). The authors concluded that, in patients with HFrEF, there was no statistically significant difference between sacubitril-valsartan and valsartan with respect to reducing NT-proBNP levels.

Although the LIFE trial has produced neutral results, some important characteristics of this study should be considered. The primary endpoint was changes in NT-proBNP levels, an important biomarker in the context of HF. However, the sample did not have sufficient statistical power to either confirm or refute benefits in hard clinical endpoints. Besides, the protocol had a clinical follow-up was of 24 weeks, which is a short period to detect a significant number of major cardiovascular events. Also, the study was interrupted due to the pandemic of COVID-19, and the *a priori* defined sample was not achieved. Finally, except for the CONSENSUS clinical trial, published in 1987, that evaluated patients without any previous treatment for HF, all other studies that proposed to evaluate patients with advanced HF (Table 1) had markedly larger samples and follow-up periods. For example, the sample size in the CIBIS-II trial,[9] which tested bisoprolol in advanced HF patients in NYHA III-IV, was 10 times greater than that in the LIFE study, allowing a more precise evaluation of the clinical benefits of the intervention.

Pharmacological treatment of advanced HF is challenging. The tolerability for drugs is usually limited by borderline blood pressure levels and renal function. Yet, we must keep on trying to implement therapeutical strategies that can potentially

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improve the natural history of this syndrome. The results of the LIFE trial may have been disappointing, but they do not completely refute the possible clinical benefits of sacubitril-valsartan in more advanced stages of HF. Besides, the definition of the stages of this condition is always a dynamic process. A patient initially classified as advanced HF, for example, can gradually improve with the implementation of therapeutical strategies and become eligible for the four pillars of HF contemporary pharmacological therapy. Thus, the establishment of pharmacological treatments in advanced HF is a continuous process in clinical practice, and the cardiologist should try as many alternatives as possible for the improvement of quality and quantity of life before opting for more advanced and definitive strategies like cardiac transplant or ventricular assist device.

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Table 1 – Comparison of the main pharmacological studies on patients with advanced heart failure

	DRUGS	N	INCLUSION CRITERIA	NYHA	MAIN RESULTS
ACE inhibitors					
CONSENSUS (1987)[10]	Enalapril vs placebo	253	NYHA IV; congestive HF, cardiomegaly at chest X-ray; without ACE inhibitors	IV (100%)	Enalapril reduced overall mortality by 40% within 6 months (26% vs 44%, p = 0.002) and by 31% in one year (52% vs 36%, p = 0.001)
Beta-blockers					
CIBIS-II (1999)[9]	Bisoprolol vs placebo	2647	18-80 years; NYHA III–IV; LVEF ≤ 35%; chronic HF; treatment with ACE inhibitors and diuretics	III–IV (100%)	Bisoprolol reduced overall mortality by 34% (12% vs 17%, p < 0.001) in NYHA III and IV patients
COPERNICUS (2001)[11]	Carvedilol vs placebo	2289	NYHA III–IV for > 2 months; LVEF < 25%; clinically euvolemic	III–IV (100%)	Carvedilol reduced overall mortality by 35% (11% vs 17%, p < 0.001); in patients < 70 or > 70 years old and LVEF < 20 or > 20%
Mineralocorticoid receptor antagonists					
RALES (1999)[12]	Spironolactone vs placebo	1663	NYHA III–IV; FEVE ≤ 35% in the last 6 months; treatment with ACE inhibitors and diuretics	III–IV (100%)	Spironolactone reduced overall mortality by 30% (35% vs 46%, p < 0.001); in patients < 67 or > 67 years old and LVEF < 26 or > 26%, NYHA III or IV
Neprilysin inhibitors and angiotensin II receptor blockers					
LIFE (2021)[8]	Sacubitril-valsartan vs Valsartan	335	NYHA IV in the last 3 months; standard treatment for HF; (LVEF) ≤35%; BNP ≥250 pg/mL or NT-proBNP ≥800 pg/mL	IV (100%)	The estimated proportional change in the NT-proBNP AUC was 0.95 (95% CI 0.84-1.08; p = 0.45). Days alive out of hospital and free from HF events: 103.2 vs. 111.2 days (p = 0.45).
Hydralazine and isosorbide dinitrate					
A-HEFT (2004)[13]	Hydralazine + isosorbide dinitrate vs placebo	1050	≥ 18 years old; NYHA III–IV for 3 months; self-reported African American; standard treatment for 3 months.	III–IV (100%)	Hydralazine + isosorbide dinitrate reduced overall mortality by 43% (6% vs 10%, p = 0.02) and hospitalizations for HF by 33% (16% vs 24%, p = 0.001) and improved quality of life scores (p = 0.02)

ACE: angiotensin converting enzyme; LVEF: left ventricular ejection fraction; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide (BNP); NYHA: New York Heart Association.

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