Editorial

Neprilysin: Indications, Expectations, and Challenges

Neprilisina: indicaciones, expectativas y retos

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Neprilysin has become a focus of interest in cardiology, due to the impressive benefits of combining neprilysin inhibition and angiotensin receptor blockade demonstrated in the recent PARADIGM-HF trial, which tested LCZ696 (now known as sacubitril/valsartan) and its associated lower dose (NEPIs) with a combination of NEPI and angiotensin II receptor blockers (ARBs), which led to a new class of drugs called angiotensin receptor neprilysin inhibitors. Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor, which has shown better-than-expected results in the PARADIGM-HF trial (Figure).

PARADIGM-HF was a multinational, randomized, double-blind study of 8442 patients. The aim was to compare sacubitril/valsartan with enalapril in adult patients with chronic heart failure (New York Heart Association [NYHA] class II-IV) and reduced left ventricular ejection fraction (LVEF < 40%, later amended to ≤ 35%), in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular death or hospitalization for heart failure. Prior to study participation, patients were treated with the standard of care therapy, which included ACEI/ARBs (> 99%), beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). The median follow-up duration was 27 months, and patients were treated for up to 4.3 years.

Patients were required to discontinue their existing ACEI or ARB therapy and enter a sequential, single-blind, run-in period. During the run-in period, they received treatment with enalapril 10 mg twice daily, followed by a single-blind treatment with sacubitril/valsartan 100 mg twice daily, which was increased to 200 mg twice daily. They were then randomized to the double-blind period of the study. During that period, they received either sacubitril/valsartan 200 mg or enalapril 10 mg, twice daily. The mean age of the population studied was 64 years, and 19% were 75 years or older. At randomization, 70% of patients were NYHA class II, 24% were class III, and 0.7% were class IV. The mean LVEF was 29%, and there were 963 (11.4%) patients with a baseline LVEF > 35% and ≤ 40%. The study was prematurely terminated, due to the overwhelming reductions in death from cardiovascular causes and the reduction in the composite primary endpoint (cardiovascular death or hospitalization secondary to heart failure). The PARADIGM-HF trial is also referred to as the 20% trial, due to the homogeneous ~20% relative reductions in all studied endpoints, including the composite primary endpoint of cardiovascular death, sudden cardiac death, and hospitalization for heart failure (Table 1).

Although sacubitril/valsartan has shown enormous promise, there are challenges and unaddressed issues that merit additional investigation.
The PARADIGM-HF study was a large-scale, randomized, phase III trial that compared sacubitril/valsartan to enalapril in patients with heart failure with reduced ejection fraction (HFrEF) characterized by symptoms of fluid retention despite optimal therapy. The study showed that sacubitril/valsartan significantly reduced the risk of cardiovascular death and hospitalization for heart failure compared to enalapril. This achievement was driven by a decrease in hospitalizations due to heart failure, a composite endpoint that included cardiovascular death, worsening heart failure, and hospitalization for heart failure. The findings were consistent across different subgroups, including patients with New York Heart Association (NYHA) class II and III heart failure, those with a history of diabetes and left ventricular ejection fraction of 30% or less. The results were supported by a favorable safety profile, with a lower risk of angioedema and hyperkalemia compared to enalapril. The study also demonstrated significant neurohormonal changes, including a 20% reduction in the levels of norepinephrine and a 19% decrease in plasma ANP (atrial natriuretic peptide) levels.

The PARADIGM-HF study was a landmark in the treatment of heart failure, providing strong evidence for the use of neprilysin inhibitors in the management of HFrEF. It paved the way for the approval of sacubitril/valsartan by regulatory agencies worldwide, including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and led to its recommendation as a first-line therapy in the management of HFrEF.

The PARADIGM-HF results also highlighted the importance of improving heart failure care and the need for continued research to explore new therapeutic strategies. The study underscored the challenges associated with maintaining adequate dosages of ACE inhibitors andARBs due to hyperkalemia and other side effects, and it provided a rationale for the development of drugs that can block the renin-angiotensin system in a more balanced manner.

Table 1: Summary of Safety Concerns for Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hypotension</th>
<th>Renal impairment</th>
<th>Hyperkalemia</th>
<th>Angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
<td>Hepatotoxicity</td>
<td>Cognitive impairment</td>
<td>Statin drug-drug interaction</td>
<td>Thrombocytopenia</td>
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<tr>
<td>Missing information</td>
<td>Pediatric patients with HF</td>
<td>Patients with severe renal impairment</td>
<td>Long-term data on sacubitril/valsartan use in HF</td>
<td>Effects in ACEI/ARB-naïve patients with HF</td>
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ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure.
and prognosis in patients with heart failure, but preserved ejection fraction, also known as HFrEF patients? Currently, there is a lack of clinical trials on HFrEF that demonstrated therapeutic benefits with agents commonly used in patients with reduced ejection fraction. Consequently, therapies for HFrEF are directed toward symptom management and cardiovascular risk factors. However, among patients with HFrEF, sacubitril/valsartan showed promising safety and efficacy results in a phase 2 trial. The PARAMOUNT trial was a randomized, double-blind, parallel-group, active controlled trial that compared sacubitril/valsartan with valsartan alone. The primary endpoint was a change from baseline in NT-proBNP at 12 weeks. The groups had similar baseline characteristics. Most patients were aged, female, overweight, and classified as NYHA class II. A greater NT-proBNP reduction was detected at week 4 in the sacubitril/valsartan group compared with the valsartan group, but it did not reach significance (P = .063). At 12 weeks, NT-proBNP was significantly reduced in the sacubitril/valsartan group compared with valsartan (P = .005). The findings from PARAMOUNT suggested that sacubitril/valsartan might have favorable effects in patients with HFrEF. Further investigation of the HFrEF population is ongoing in the PARAGON study, a multicenter, randomized, double-blind, parallel group, active controlled study. That study aims to evaluate the efficacy and safety of sacubitril/valsartan compared with valsartan on morbidity and mortality in patients with heart failure (NYHA class II-IV) and preserved ejection fraction.

Last, but not least, very recently, circulating soluble neprilysin (sNEP) was proposed as a putative biomarker. At present, data on sNEP have suggested that it may play a prognostic role in both chronic and acutely decompensated heart failure, but in HFrEF results are controversial. Interestingly, circulating sNEP was shown to be catalytically active. Moreover, a recent report demonstrated that sNEP might even be superior to NT-proBNP as a surrogate prognostic biomarker of the neurohormonal axis in heart failure. Further refinements in sNEP assays are mandatory before its introduction to clinical practice. However, the data reported to date suggest that it may become a valuable tool for patient prognostication and eventually therapy guidance.

As an epilogue, the cost of the treatment with this new agent is likely to represent a barrier to its use in everyday real-life clinical practice, since the cost of effective agents such as the ACEI enalapril is very low (comparable to the cost of chewing gum in many countries). Conceivably, the implementation of a biomarker-driven strategy may be proposed to preferentially switch from ACEI treatment to Entresto in the sickest patients. Along these lines, it is noteworthy that the use of natriuretic peptides was among the inclusion criteria in the PARADIGM-HF trial. The cost-effectiveness and cost per quality-adjusted life year gained of sacubitril/valsartan relative to enalapril for treatment of HFrEF deserve intensive research in real-world scenarios adjusted by country and health care system.15

CONFLICTS OF INTEREST

A. Bayes-Genis and J. Lupón have applied for a patent for sNEP as a prognostic biomarker, which is pending approval. A. Bayes-Genis has lectured and participated in Advisory Boards from Novartis.

REFERENCES