Sacubitril/Valsartan: A Pioneer in Acute Heart Failure and a Paradigm in Chronic Heart Failure

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Abstract

Sacubitril/valsartan (neprilysin inhibitor/angiotensin receptor blocker combination) was compared to enalapril in stable patients who had heart failure with reduced ejection fraction (HFrEF) in the PARADIGM-HF trial [1]. In the 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less, this combination resulted in the primary outcome (a composite of death from cardiovascular causes or hospitalization for heart failure) in 21.8% of patients compared to 26.5% of patients in the enalapril group. As compared with enalapril, this combination also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The main risks of this therapy were hypotension and angioedema.

The current issue of the New England Journal of Medicine [2] reported the findings of the PIONEER-HF clinical trial, which examined the role of angiotensin–neprilysin inhibition in acute decompensated heart failure.

Methods

- HfrEF patients who were hospitalized for acute decompensated heart failure were included.
- After hemodynamic stabilization, patients were randomly assigned to receive sacubitril–valsartan (97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (10 mg twice daily).
- The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration from baseline through weeks 4 and 8.
- Key safety outcomes were the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

Results

- 881 patients were randomized:
  - 440 sacubitril–valsartan
  - 441 enalapril.
- Time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group
- The greater reduction in the NT-proBNP concentration with sacubitril–valsartan than with enalapril was evident as early as week 1.
- Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.

Conclusion

Among patients with heart failure with reduced ejection fraction (HFrEF) who were hospitalized for acute decompensated heart failure, the

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initiation of sacubitril–valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy.

Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.

Clinical Implications

Heart failure remains a very common and lethal disease, associated with enormous cost, mostly from hospital admissions, despite recent novel pharmacologic and nonpharmacologic advances in its treatment [3]. The concept of neprilysin inhibition in combination with angiotensin receptor inhibition is novel, and appears to have gained an important niche in the guideline-directed treatment of heart failure with reduced ejection fraction [4]. Nevertheless, it remains very important to address medication adherence in the treatment of heart failure [5] especially in light of the soaring costs of heart failure medications [6] and the polypharmacy expected to achieve better outcomes [7]. Patient-centered therapy, examining “what works best” taking into consideration these factors may ultimately provide the desired outcomes [8].

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