駆出率の保たれた心不全は依然として治療が困難である

PARAGON-HF試験では駆出率の保たれた心不全におけるエンドポイントは達成できなかったが、一部の患者で有益性が認められた

PARAGON-HF misses endpoint in heart failure with preserved ejection fraction, but benefit noted in some patients

アンジオテンシン受容体-ネプリライシン阻害薬sacubitril/バルサルタンは、駆出率の保たれた心不全患者（HFpEF）における全入院および心血管死減少からなる一次エンドポイントは達成できなかったが、データから一部の患者群において有益である可能性が示された。一次エンドポイント率比は0.87（95% 信頼区間 [CI] 0.75-1.01；p=0.059）であった。駆出率中央値57%未満の患者において有益性が高く、一次エンドポイントが22% 低下し、さらに女性では28% 低下した。このPARAGON-HF試験の結果は、ESC Congress 2019のHot Line Session で発表され、*New England Journal of Medicine* に掲載された。

Full Text

The angiotensin neprilysin inhibitor sacubitril/valsartan missed its primary endpoint of reducing total hospitalization and cardiovascular death in patients with heart failure with preserved ejection fraction (HFpEF), but the data suggest there may be benefit in some patient groups. The late breaking results of the PARAGON-HF trial were presented in a Hot Line Session at ESC Congress 2019 together with the World Congress of Cardiology and published in the *New England Journal of Medicine*.

The PARAGON-HF trial showed evidence of a heterogeneous response to treatment, with potential benefit in certain subgroups, such as women and patients with an ejection fraction below the median. "Our data strongly imply that one size might not fit all in HFpEF," said co-principal investigator Professor Scott D. Solomon of Brigham and Women's Hospital, Harvard Medical School, Boston, US.
Up to 64 million worldwide have heart failure – of these approximately half have left ventricular ejection fraction of 40% or greater. This encompasses heart failure with mid-range ejection fraction (HFmrEF; ejection fraction 40–49%), and HFpEF (ejection fraction 50% or greater). Evidence- based therapies exist only for heart failure with reduced ejection fraction (HFrEF; ejection fraction 40% or less).

Sacubitril/valsartan, which combines the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan, simultaneously inhibits the renin-angiotensin system and augments endogenous vasoactive peptide systems. The drug reduced morbidity and mortality in patients with HFrEF in the PARADIGM-HF trial. It has a class I guideline recommendation for the treatment of HFrEF.

PARAGON-HF was designed to test the hypothesis that sacubitril/valsartan would improve outcomes in HFpEF. A total of 4,822 patients were randomly assigned to sacubitril/valsartan or valsartan. The comparator was valsartan because most HFpEF patients already take a renin-angiotensin system inhibitor. Patients were required to have signs and symptoms of heart failure, a left ventricular ejection fraction of 45% or greater, evidence of natriuretic peptide elevation, and structural heart disease. The median follow-up was 34 months. The primary endpoint was a composite of total (first and recurrent) heart failure hospitalizations and cardiovascular death.

The rate ratio for the primary endpoint was 0.87 (95% confidence interval [CI] 0.75–1.01; p = 0.059). This reduction was just short of statistical significance and was driven by a decline in heart failure hospitalization with no effect on cardiovascular death or all-cause mortality.

A number of sensitivity analyses, including assessment of investigator-reported outcomes, favored sacubitril/valsartan. Several secondary endpoints, such as quality of life, change in New York Heart Association (NYHA) class, and percentage of patients with worsening renal function, favored sacubitril/valsartan. Prof Solomon said: "The reduction in total hospitalizations for heart failure was smaller than anticipated and not statistically significant. However, some secondary endpoints suggested a modest overall benefit with sacubitril/valsartan."

Sacubitril/valsartan was associated with more hypotension, but less hyperkalemia and less renal dysfunction compared with valsartan, findings similar to those seen in the PARADIGM-HF trial.

Importantly, there was heterogeneity in the population with respect to treatment response. In particular, there was greater benefit in patients with ejection fraction below the median of 57%, with a 22% reduction (rate ratio 0.78; 95% CI 0.64–0.95) and in women, with a 28% reduction (rate ratio 0.73; 95% CI 0.59–0.90) in the primary endpoint. "Our data suggest that there may be differential benefit, with some patients, including those in the lower range of ejection fraction and women responding to a greater degree than others," said Prof Solomon.

He noted that the results at the lower end of the ejection fraction range should be considered in light of the PARADIGM-HF trial which showed substantial benefit in those with heart failure and ejection fraction below 40%. Aside from ejection fraction, the entry criteria for PARADIGM-HF and PARAGON-HF were nearly identical. "Our findings indicate that the benefit of sacubitril/valsartan observed in PARADIGM-HF could extend to heart failure patients with ejection fraction below the normal range, including those designated HFmrEF," he said.

As for the observations in women, Prof Solomon said: "The potential differential benefit in women is intriguing as women make up a much greater proportion of patients with HFpEF compared to HFrEF. Further analyses will explore these subgroup findings in detail and help determine which patients with heart failure across a broad range of ejection fraction might benefit the most from sacubitril/valsartan."

The study was funded by Novartis. Dr. Solomon has received research grants through his institution from Novartis for the conduct of the PARAGON-HF trial and has consulted for Novartis.

Conference News