CHFS'S PERSPECTIVE ON HEART FAILURE TRIALS RELEASED AT ESC 2019

REVIEW OF PARAGON-HF

PARAGON-HF is the largest clinical trial in heart failure with preserved ejection fraction (HFpEF) conducted to date, and is the latest trial, in a long list, looking at the clinical effectiveness of different treatments for HFpEF patients. HFpEF remains one of the greatest and most challenging unmet needs in cardiovascular medicine. PARAGON-HF, a Phase III trial, compared the long-term efficacy and safety of sacubitril/valsartan versus valsartan in 4,822 patients with HFpEF.

While the trial missed statistical significance on its composite primary endpoint of reducing cardiovascular death and total heart failure hospitalizations, there was heterogeneity in the population with respect to treatment response. "*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 Professor Solomon. Indeed, 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). "*The potential differential benefit in women is intriguing as women make up a much greater proportion of patients with HFpEF compared to HFrEF*" said Dr. Solomon.

Several secondary endpoints, such as quality of life, change in New York Heart Association (NYHA) class, and percentage of patients with worsening renal function, favoured sacubitril/valsartan.

Safety and tolerability were consistent with previously reported sacubitril/valsartan data.

PARAGON-HF results aligned with previous landmark HFpEF trials suggesting that the definition of HFmrEF (heart failure with mid-range ejection fraction) and HFpEF should be revisited.

CHFS's take on the outcomes: Certainly, there is much more to understand about HFpEF and those patients with mid-range EF. This is the first time a major HFpEF clinical trial included an active comparator group and, like many RCTs before, had pre-defined echocardiographic and natriuretic peptide criteria for enrollment. The trial also excluded 44% of patients who were potentially eligible and, similarly to PARADIGM, there was a run-in phase that resulted in a further 9% of patients being excluded – hence generalizability will need to be considered in clinical practice. Any of the secondary outcomes should be considered hypothesis-generating given the neutrality of the trial. The PARAGON trial will influence future clinical trials design in patients with HFpEF and women will continue to be well represented in these trials.

References

Solomon S, Rizkala A, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5(7):471-482. doi: 10.1016/j.jchf.2017.04.013.