Editorial Comment

PARAGON-HF - considerations for potential use of sacubitril-valsartan in real-world heart failure with mildly reduced ejection fraction

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Recently, the results of the much anticipated Prospective Comparison of ARNI [angiotensin receptor−neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial were published,[1] showing that in patients with HFpEF (symptomatic HF, left ventricular EF ≥45%, structural heart disease, and elevated natriuretic peptides), sacubitril/valsartan compared to valsartan did not significantly improve the primary outcome of cardiovascular death or total HF hospitalizations (rate ratio 0.87; 95% confidence interval 0.75-1.01; p=0.06). In this issue of Journal of Cardiac Failure, Sayeed et al.[2] used the Get With The Guidelines − HF (GWTG-HF) registry to assess eligibility for sacubitril/valsartan based on PARAGON-HF inclusion/exclusion criteria, and observed that among patients with HFpEF, 10.3% met strict criteria and 71.3% met "broad" criteria, defined as a minimum set of inclusion/exclusion criteria with which clinicians might consider sacubitril/valsartan in clinical practice. This analysis has several obvious limitations. Specifically, the authors assessed hospitalized patients whereas PARAGON excluded those with "acute decompensated HF"; did not have access to key eligibility criteria in PARAGON such as structural heart disease (although these criteria are met by a majority of patients with HFpEF); and lacked information on a large number of variables considered both in PARAGON and by the prudent provider in making treatment decisions, e.g. severe comorbidity such as dementia, cancer, pulmonary disease or frailty. Is the PARAGON trial and the eligibility assessment relevant?

Yes, we believe the trial and the eligibility findings will affect clinical practice, but modestly and inconsistently. In clinical treatment decisions, multiple factors are considered. Formal factors include guideline recommendations, regulatory agency labelling, and payer reimbursement policies.[3] Informal factors include (1) patient and provider assessment of the "whole picture", which may be determined by patient awareness and agency and clinical specialty and knowledge base of the provider, (2) the clinical meaningfulness of the trial outcomes and magnitude of the relative and absolute risk reduction, (3) biological plausibility of a true effect, including the likelihood of a type II error ("false negative"), and relevance of patient sub-group and secondary outcomes, (4) supporting evidence outside of the main trial(s), (5) real and perceived cost and cost effectiveness (not the same thing), and (6) as assessed by Sayeed et al., whether patients in the trial(s) are representative of the "real world" (i.e. generalizability).

PARAGON-HF will be discussed extensively in the foreseeable future but we cannot refrain from mentioning a few salient observations. The p-value of 0.06 did not meet the 0.05 criterion but there were statistically significant interactions with EF and with sex, suggesting a benefit in patients with EF ≤median (EF ≤57%; risk ratio 0.78 [0.64-0.95]; similar to the effect in HFrEF in PARADIGM-HF) but no benefit with EF >median, and a benefit in women (which may be a chnace finding or related to higher "normal" EF in women, different natriuretic peptide physiology, and/or other factors). As a consequence, sacubitril/valsartan will not be used in truly normal EF (whether the lower limit of normal is 50% or 55% or even higher, especially in women). The benefit in "mildly reduced" or "lower than normal" EF was from a sub-group and should be interpreted with caution, especially since the overall trial did not meet statistical significance for the primary endpoint. However, the EF analysis was pre-specified, and the benefits make biological sense (patients with HF and "mid-range" EF, HFmrEF, are overall clinically similar to HFrEF and different from HFpEF),[4,5] are supported by a benefit in "adjacent" HFrEF in PARADIGM-HF and are consistent with effects of other neurohormonal inhibitors and modulators in HFmrEF.[5-7] Thus we believe it is reasonable to expect that sacubitril/valsartan will be perceived as effective and indeed used in some patients with HF and mildly reduced EF.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.11.017

But is the PARAGON-HF trial generalizable? HFpEF trials use inclusion and exclusion criteria to ensure the diagnosis of HFpEF, enrich for high risk of presumably modifiable cardiovascular events and low risk of presumably non-modifiable non-cardiovascular events, and if possible, target a phenotype most likely to respond to the tested intervention.[8] Despite its limitations, the analysis of GWTG-HF by Sayeed et al. suggests that far from all but a substantial proportion of patients may be reasonable candidates for sacubitril/valsartan. The crude assessment suggested that among patients with HFpEF (defined as EF>40%), 71.3% had eGFR ≥30 ml/min/1.73 m2, systolic blood pressure ≥100 mm Hg, and not "advanced HF". Is this enough to justify use of sacubitril/valsartan? Given the poor implementation of sacubitril/valsartan in HFrEF,[9] despite the overwhelmingly positive PARADIGM-HF and reasonably high eligibility in real world HFrEF patients,[10] and incidentally, the poor implementation of HFrEF therapy in general, it is likely that far from 71.3% of patients with HFmrEF will be considered in clinical practice. In contrast, only 10.3% met strict PARAGON-HF criteria. Many of these criteria do not preclude a therapeutic benefit (if there is one) and thus reasonable use had the trial been positive might be higher than 10.3%. So what will use of sacubitril/valsartan in HFmrEF be, and what should it be?

We predict that it will be much closer to 10% than 70% of patients with HFmrEF, but we do so not based on the eligibility analysis by Sayeed et al., but on very complex considerations by multiple stakeholders of factors such as the current lack of alternative therapy in HFmrEF, the equivocal findings in PARAGON-HF, the barriers to implementation of HF care in general, clinician inertia, and perceptions of suitable patient phenotypes and magnitude of perceived potential effect on relevant end-points. If HFpEF therapeutics were previously complex, PARAGON-HF and the eligibility analysis published in this issue of the Journal have not made the situation less complex, but rather more energized.

Conflicts of Interest

Dr. Lund reports personal fees from Merck, grants from Boehringer Ingelheim, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, grants and personal fees from Novartis, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, personal fees from Medscape, outside the submitted work.

Dr. Savarese reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, grants from MSD, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, outside the submitted work.

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