REVIEW ARTICLE

Heart failure with preserved ejection fraction after the PARAGON-HF trial results: current knowledge and future directions

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KEY WORDS
heart failure, preserved ejection fraction, sacubitril / valsartan

ABSTRACT
Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition, particularly in the context of the aging of the population. HFpEF is associated with high morbidity, mortality, and rate of heart failure rehospitalization as well as poor quality of life. Previous studies on HFpEF failed to reach a positive outcome. There is currently no approved treatment for HFpEF. The overall PARAGON-HF trial population showed a 13% reduction in the primary endpoint (cardiovascular death and total heart failure hospitalizations) with sacubitril / valsartan treatment as compared with valsartan, which was of borderline statistical significance. Analyses of the secondary endpoints, including the clinical status, quality of life, and kidney function, imply that sacubitril / valsartan offers benefits compared with valsartan alone. The results of the PARAGON-HF trial revealed that patients with HFpEF and particular clinical profiles (lower strata of ejection fraction below 57% and female sex), for whom no evidence-based therapy is available, may benefit from treatment with sacubitril / valsartan. This review article summarizes opinions on the PARAGON-HF results as well as a mechanistic discussion.

Introduction Around half of all patients with heart failure (HF), that is, approximately 13 million people worldwide, are estimated to have heart failure with preserved ejection fraction (HFpEF). There is currently no approved treatment for HFpEF[1] and there were few HFpEF trials over the years (FIGURE 1). This review article presents an ongoing discussion after the PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in HFpEF) trial, and provides appropriate comments for clinicians.

Discussion on the results of the PARAGON-HF trial HFpEF is an increasingly common condition, particularly with the aging of the population, and is associated with high morbidity and mortality.[1] It is also associated with poor prognosis, low quality of life, and high rates of rehospitalization, and remains a public health problem. Previous studies in HFpEF testing neurohumoral inhibition (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or mineralocorticoid receptor antagonists) did not show any benefits when the drugs tested were compared with placebo (FIGURE 1). The last 2016 European Society of Cardiology guidelines for heart failure recommend diuretics in HFpEF to improve congestion and treat cardiovascular and noncardiovascular comorbidities.[1]

The PARAGON-HF trial (funded by Novartis; ClinicalTrials.gov identifier: NCT01920711) was a randomized, double-blind, parallel-group trial on HFpEF that for the first time included an active comparator (valsartan). The inclusion and exclusion criteria are presented in TABLE 1. The PARAGON-HF trial is the largest HFpEF trial[2] (TABLE 2)with very effective retention of patients. Only 7 patients withdrew their consent and 2 patients were lost to follow-up. Baseline characteristics of the PARAGON-HF population and cohorts with HFpEF from earlier studies are presented in TABLE 2.

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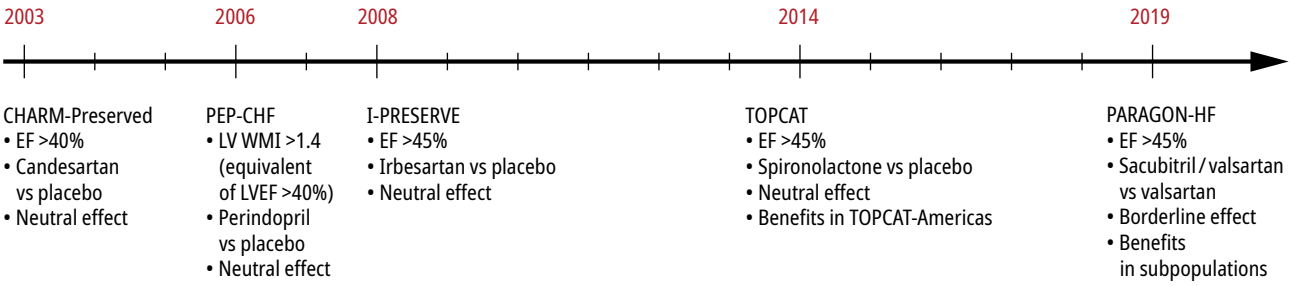

FIGURE 1 The timeline of HFpEF trials and the effect on the primary endpoints[3-7]
Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; WMI, wall motion index

TABLE 1 **The inclusion and exclusion criteria of the PARAGON-HF trial**[2]

Key inclusion criteria	Key exclusion criteria
Age ≥50 y, LVEF ≥45%	History of LVEF <40%
Symptoms of HF requiring treatment with diuretic(s) for ≥30 days prior to study entry	Current acute decompensated HF
Current symptomatic HF (NYHA class II–IV)	SBP <110 mm Hg or ≥180 mm Hg at baseline
Structural heart disease (LAE and/or LVH)	SBP >150 mm Hg and <180 mm Hg at Visit 1 unless the patient is receiving 3 or more antihypertensive drugs
1) a HF hospitalization within 9 months prior to Visit 1 and NTproBNP >200 pg/ml for patients with sinus rhythm or >600 pg/ml for patients in atrial fibrillation at Visit 1, or 2) NTproBNP >300 pg/ml for patients with sinus rhythm or >900 pg/ml for patients with atrial fibrillation	Serum potassium >5.2 mmol/l at baseline
–	eGFR <30 ml/min/1.73 m^2 at baseline

Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; LAE, left atrium enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hyperthropy; NYHA, New York Heart Association; NTproBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure

In the PARAGON-HF trial, the primary outcome was composed of total hospitalizations for heart failure (both first and recurrent) and death from cardiovascular causes.[2] Secondary outcomes included NYHA class change from baseline to 8 months, worsening renal function defined as a decrease in the estimated glomerular filtration rate of 50% or more, end-stage renal disease, or death due to renal failure, change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score from baseline to 8 months (scale from 0 to 100; higher scores indicate fewer symptoms and physical limitations), and death from any cause.[7]

The primary composite endpoint (TABLE 3), an event rate with sacubitril/valsartan of 12.8 per 100 patient-years (PY), as compared with 14.6 per 100 PY with valsartan, contributed to a rate ratio (RR) of 0.87 (95% CI, 0.753–1.005; P = 0.06).[7] There was a modest and statistically nonsignificant lower rate of hospitalizations for HF in patients treated with sacubitril/valsartan than in those treated with valsartan alone. There were 690 and 797 total hospitalizations for HF, respectively (RR, 0.85; 95% CI, 0.72–1). No differences between the sacubitril/valsartan group and the valsartan group were found regarding the risk of death from cardiovascular causes (8.5% and 8.9%, respectively; hazard ratio [HR], 0.95; 95% CI, 0.79–1.16) or in all-cause mortality (14.2% and 14.6%, respectively; HR, 0.97; 95% CI, 0.84–1.13; P = 0.68).[7]

In the PARAGON-HF trial, a different primary endpoint was used than in previous HFpEF trials. While previous studies had evaluated time to cardiovascular death or first hospitalization due to HF, the PARAGON-HF trial focused on cardiovascular death and both first and recurrent hospitalizations. It was based on a post hoc analysis of the negative CHARM-Preserved study of candesartan, which suggested it to be beneficial if recurrent hospitalizations were taken into account and related to better identifying the benefit for the high-risk population.

In the PARAGON-HF trial, 3 of 4 prespecified secondary outcomes, which were considered to be exploratory, were significant.[7] The first outcome was a change in the NYHA class from baseline to 8 months. In 15% of patients from the sacubitril/valsartan group, the NYHA functional class improved, in 76.3%, it remained unchanged, and in 8.7%, it worsened. In the valsartan group, these percentages were 12.6%, 77.9%, and 9.6%, respectively (OR for improvement, 1.45; 95% CI, 1.13–1.86; P = 0.004). However, the majority of patients were in the NYHA class II. The second outcome was declined renal function, which favored sacubitril/valsartan over valsartan alone (1.4%

TABLE 2 Characteristics of the study populations in trials on heart failure with preserved ejection fraction

Characteristic		PARAGON-HF (n = 4822)	TOPCAT-Americas (n = 1767)	I-PRESERVE (n = 4128)	CHARM-Preserved (n = 3023)	PEP-CHF (n = 850)
Age, y		73 (8)	72 (64–79)	72 (7)	67 (11)	75 (72–79)
Women		52	50	60	40	56
NYHA class	II	72	59	21	61	–
	III	27	35	76	37	–
	I/II	–	–	–	–	75
Race	White	82	78	93	92	–
	Black	2	17	2	4	–
	Asian	13	1	1	2	–
	Other	3	4	4	2	–
Ejection fraction		58 (8)	58 (53–64)	–	–	64 (56–66)
Systolic blood pressure, mm Hg		136 (15)	129 (118–138)	136 (15)	136 (18)	139 (129–150)
Diastolic blood pressure, mm Hg		77 (11)	70 (62–80)	79 (9)	78 (11)	80 (74–86)
Body mass index, kg/m^2		30 (5)	33 (28–38)	30 (5)	29 (6)	28 (25–30)
Hypertension		96	90	89	64	79
Coronary artery disease		43	32	13	33	PCI 8
						CABG 20
Myocardial infarction		23	20	23.5	44	27
Atrial fibrillation at baseline		32	34	29	29	21
History of atrial fibrillation[a]		52	42	29	29	–
Diabetes mellitus		43	45	27	28	21
Stroke		10	9	10	9	–
Prior HHF		48	59	23	69	–
eGFR	≥60 ml/min/1.73 m^2	53	52	–	–	–
	≥45 ml/min/1.73 m^2, <60 ml/min/1.73 m^2	29	31	31	–	–
	<45 ml/min/1.73 m^2	18	17	–	–	–

Data are presented as percentage, mean (SD), or median (interquartile range).

a History of atrial fibrillation and at screening in sinus rhythm on electrocardiography

Abbreviations: CABG, coronary artery bypass grafting; HHF, hospitalization for heart failure; IQR; interquartile range; PCI, percutaneous coronary intervention; others, see FIGURE 1 and TABLE 1

TABLE 3 Primary outcomes in the PARAGON-HF trial[7]

Outcome	Sacubitril/valsartan (n = 2407)	Valsartan (n = 2389)	Ratio rate or hazard ratio (95% CI)
Primary composite outcome (adjudicated)[a]	894 (37)	1009 (42)	0.87 (0.75–1.01)
Death from cardiovascular causes	204 (8.5)	212 (8.9)	0.95 (0.79–1.16)
Total hospitalizations for heart failure	690 (28.5)	797 (33.4)	0.85 (0.72–1)

Data are presented as number (percentage) of patients unless otherwise indicated.

a The primary analysis was based on the model of Lin et al[8] and the composite outcome was adjudicated with total hospitalizations for heart failure including first and recurrent events.

vs 2.7%; HR, 0.5; 95% CI, 0.33–0.77; P = 0.002). The third significant secondary outcome was the improvement in the KCCQ greater than 5 points with 33% in the sacubitril/valsartan group as compared to 29.6% in the valsartan group (OR, 1.3; 95% CI, 1.04–1.61; P = 0.02). At 8 months, the mean change in the KCCQ clinical summary score was 1 point (95% CI, 0–2.1).

With regards to the 12 prespecified subgroups, in the group in which sex was the criterion of the analysis, female patients (RR for primary composite endpoint, 0.73; 95% CI, 0.59–0.9), seemed to benefit more from sacubitril/valsartan than male patients (RR for primary composite endpoint, 1.03; 95% CI, 0.85–1.25).[3,4] Similarly, in the subgroup regarding ejection fraction (EF), those with left ventricular ejection fraction (LVEF) equal to or lower than the median (57%) benefited more for primary composite endpoint (RR, 0.78; 95% CI, 0.64–0.95) than those with LVEF higher than the median (RR, 1; 95% CI, 0.81–1.23).[7] However, the performed analyses did not provide a definite mechanistic basis for these findings.

The treatment effect of sacubitril/valsartan, however, was heterogeneous, more beneficial for patients with EF below normal, and in women rather than in men.[7,9] These 2 groups showed an absolute risk reduction similar to that seen in patients with EF of less than 40% in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial. The effect of sacubitril/valsartan was also modified by LVEF in the analysis of both the PARADIGM-HF and the PARAGON-HF trials (treatment-by-continuous LVEF interaction; P = 0.02).[10] The results of the PARAGON-HF suggest that some patients with HFpEF, for whom no evidence-based therapy is available, may benefit from treatment with sacubitril/valsartan. It is not the first time that a drug that is effective in heart failure with reduced ejection fraction (HFrEF) is also effective in patients with mild systolic dysfunction (EF, 40%–49%)—spironolactone, β-blockers. Of note, EF of 40% is an arbitrary cutoff point and the limitations of LVEF measurements are well known.

It is also well known that patients with a recent hospitalization for HF are at high risk for clinical progression and death. Another publication from the PARAGON-HF trial provides important data about the period from HF hospitalization and benefits of sacubitril/valsartan as compared with valsartan.[11] Out of f 4796 randomized patients in the PARAGON--HF trial, 2490 (52%) had no previous HF hospitalization. Within the median of 35 months of the follow-up period, it was revealed that the risk of total HF hospitalizations and cardiovascular death was inversely and nonlinearly associated with time from prior HF hospitalization (P <0.001).

The relative reduction in the risk of primary events was highest in patients hospitalized within the last 30 days and lowest in those who were never hospitalized: the sacubitril/valsartan group as compared with the valsartan group, respectively: RR, 0.73; 95% CI, 0.53–0.99 (the rate of total primary events, 20.3) and RR, 1; 95% CI, 0.80–1.24 (the rate of total primary events, 8); relative risk reduction, $P_{\text{interaction}}$ = 0.15. For valsartan alone, the rate of total primary events was 26.7 for patients hospitalized in the previous 30 days, and 7.9 for those not previously hospitalized per 100 PY.

In comparison with valsartan, absolute risk reductions with sacubitril/valsartan were the highest in patients enrolled early after hospitalization: 6.4% (≤30 days), 4.6% (31–90 days), while no risk reduction was observed in patients screened >180 days or who were never hospitalized (trend in absolute risk reduction, $P_{\text{interaction}}$ = 0.05).[11]

In the PARAGON-HF trial, there was no benefit for sacubitril/valsartan in the total population and the results of the primary endpoint were of borderline statistical significance. Also, the construction of the PARAGON-HF trial with a run-in phase is of importance. The exclusion of higher-risk patients and those who could not take the trial drugs because of side effects might have had an impact on the results.

Heterogeneity of the population with HFpEF is well known and was also confirmed by echocardiographic findings.[12] Left ventricular hypertrophy, elevated left- and right-sided pressures and pulmonary artery systolic pressure as well as right ventricular enlargement were independently associated with HF hospitalization or cardiovascular death in the PARAGON-HF trial, while such associations were not observed for LVEF or left atrial size (P >0.05).

Safety and tolerability of sacubitril/valsartan in the PARAGON-HF trial were similar as in the PARADIGM-HF trial, with a higher prevalence of hypotension (15.8% vs 10.8%; P <0.001), but lower serum creatinine and potassium concentrations in the sacubitril/valsartan group as compared with the valsartan group.[7] In the PARAMOUNT-HF trial, the first trial with sacubitril/valsartan in HFpEF,[13] a 36-week sacubitril/valsartan therapy was associated with higher probability of preservation of estimated glomerular filtration rate in comparison with valsartan therapy.[14] In the PARAGON-HF trial, in the secondary endpoints, the risk of impaired renal function was smaller in the arm treated with sacubitril/valsartan than with valsartan alone.[7] Damman et al[15] observed that initiating inhibitors of the renin–angiotensin–aldosterone system (RAAS) in HFpEF was associated with an increase in creatinine levels, which in turn contributed to worse prognosis. In the light of the above facts, this observation appears to be

of high importance. The higher (however, very low in general) incidence of angioedema was observed in the sacubitril/valsartan group (0.6% vs 0.2%; $P = 0.02$) and the cases were milder without airway compromise.[7]

The PARAGON-HF trial is the first trial in HFpEF with an active comparator. Sacubitril/valsartan was tested against valsartan because most patients were receiving an inhibitor of the RAAS before enrolment (96% had arterial hypertension),[2] which made a placebo-controlled trial impractical. Recently, the putative placebo analysis was published[16] with data from the PARADIGM-HF and the PARAGON-HF trials (n = 13 194) and also the CHARM-Preserved and the CHARM-Alternative trials (n = 5050) with candesartan. Compared with putative placebo, sacubitril/valsartan was associated with a RR of 0.54 (95% CI, 0.45–0.65; P <0.001) for the primary endpoint across the range of LVEF with attenuation above 60%, and also with a RR of 0.67 (95% CI, 0.58–0.78; P <0.02) for the first HF hospitalization; for cardiovascular death, RR was 0.76 (95% CI, 0.64–0.89; P <0.02), and for all-cause death, RR was 0.83 (95% CI, 0.71–0.96; P <0.02).[16] The putative analysis supported the benefit of sacubitril/valsartan therapy for LVEF up to 60%. However, the results of the PARAGON-HF trial suggest further studies of angiotensin receptor neprilysin inhibitors (ARNIs) in heart failure with midrange ejection fraction (HFmrEF)/slightly reduced EF.

Mechanistic discussion The status of sacubitril/valsartan in HFrEF is well known,[1,17] and since the last guidelines, many studies of the first experiences[18] and real-world evidence structure have been published. However, HFpEF is a different story; it is highly heterogenous. There is no mechanistic explanation of the PARAGON-HF results. From the guidelines perspective, this trial enrolled patients with both HFpEF and HFmrEF. In a recent pooled analysis of the PARADIGM-HF and the PARAGON-HF trials, Solomon et al[10] demonstrated better outcomes regarding all examined endpoints in the sacubitril/valsartan group than RAAS inhibition alone. Several post hoc analyses suggested that RAAS inhibition has positive effects in HFmrEF. In the pooled analysis of these 2 trials, the therapeutic effects of sacubitril/valsartan differed with LVEF with respect to composite total hospitalizations and cardiovascular death, especially in slightly reduced ejection fraction.[10] The results of the PARAGON-HF trial imply benefits for women and those with lower LVEF. The explanation of diminished therapeutic response to sacubitril/valsartan among patients with LVEF above 57% is unclear. The population with heart failure and higher EF may demonstrate a distinct pathology and less effective neurohormonal inhibition. Amyloidosis deposition, which is present in 15% to 20% of cases with HFpEF, is considered a potential disease in this population.[19] However, amyloidosis is rare and frequently misdiagnosed.[20]

Other key issues are sex differences, common in patients with HFpEF.[21] Some researchers report a less pronounced effect of angiotensin-converting enzyme inhibitors in women than in men with HF.[22,23] However, there are also studies suggesting that angiotensin II receptor blockers, for example, valsartan, may have a more pronounced effect in women than in men.[23] Thus, the difference between men and women in the PARAGON-HF trial cannot be due to exclusively sacubitril but also to valsartan. On the other hand, in the VALIANT (Valsartan in Acute Myocardial Infarction) trial and the Val-HeFT (the Valsartan Heart Failure Trial) there were no sex-related interactions with valsartan.[24,25]

When we consider the treatment in the PARAGON-HF population, it seems that women were less intensively treated (less diuretic therapy and mineralocorticoid receptor antagonists),[9] so sacubitril/valsartan with its diuretic action could offer more benefits to women than to men. Another issue is arterial stiffness, which is age- and sex-related. Age-related arterial stiffening is more common in women than in men,[26] and it is considered a key pathophysiological factor in HFpEF. Ventricular loading is greater in women than in men, so sacubitril/valsartan could have a beneficial effect in this group due to its more hypotensive action than valsartan. Recently, in a subgroup analysis from the PARAGON-HF trial, the reduction of systolic blood pressure under treatment with sacubitril/valsartan was more pronounced among women than men (6.3 vs 4 mm Hg; $P_{\text{interaction}} = 0.005$), but that pressure reduction does not account for the beneficial effect of the therapy with sacubitril/valsartan over valsartan.[27]

Also in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial[28] in women, ventricular-vascular stiffening was the most significant determinant of outcome, whereas in men, the overall survival was influenced by heart rate and B-type natriuretic peptide. This highlights sex differences in the pathophysiology and outcomes of HFpEF and needs to be studied further. Although central aortic stiffness did not decrease after the administration of sacubitril/valsartan in HFrEF,[29] patients with HFpEF are a completely different population (hypertrophy of the left ventricle with diastolic dysfunction, hypertrophy of the arteries) and should not be compared with HFrEF in that aspect.

Another speculation regards the greater impact of atrial fibrillation on outcomes in women with HFpEF, which was revealed in the TOPCAT trial.[30] The association between atrial fibrillation and HF hospitalization was

stronger in women (HR, 1.63; 95% CI, 1.40–1.91) than in men (HR, 1.37; 95% CI, 1.18–1.58; $P_{interaction}$ = 0.03). Also, Goyal et al[21] confirmed that atrial fibrillation is an important variable in HFpEF only in women. In the PARAGON-HF trial, 81% of women had a history of atrial fibrillation or had atrial fibrillation or atrial flutter on screening.[9] Thus atrial fibrillation could contribute to a worse female prognosis in this trial.

Finally, higher body mass index (BMI) in women than in men may also play an important role. Obesity is more often observed in women with HFpEF, and also in the PARAGON-HF trial, BMI was higher in women than in men (respectively BMI >30 kg/m^2, 51% vs 47%; P = 0.001, abnormal waist circumference, 83% vs 62%; P <0.001)[7] and lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in women despite worse HF symptoms might be related to obesity. Obesity-related HFpEF is a growing phenotype of heart failure. Two central pathophysiological abnormalities in obesity-related HFpEF commonly occur: sodium retention and systemic inflammation. Features of this phenotype appear to be related to the adipocyte-derived cell signaling, including neprilysin.[31,32] Thus, this explanation of the mechanistic background regarding results of sacubitril/valsartan in patients with HFpEF seems to be of great importance.

However, in the PARAGON-HF trial, the baseline NT-proBNP level strongly predicted HF events (primary endpoint, all-cause death, cardiovascular death, and total HF hospitalization; P <0.001 for all) but did not modify the treatment response to sacubitril/valsartan compared with valsartan ($P_{interaction}$ = 0.96), and sacubitril/valsartan reduced the level of NT-proBNP by 19% relative to valsartan irrespectively of sex and LVEF.[33]

Generally, HFpEF is complex, multifactorial, and clinically heterogeneous, and it probably requires a phenotype-specific HF treatment strategy, as discussed by Upadhya and Kitzman[34] and also by Van Spall and Mamas[35] who additionally indicated healthcare services as important strategy in improving clinical outcomes in HF. It is unlikely that one drug in HFpEF could be beneficial for the whole population with the disease. This indicates the need for the next studies in HFpEF to target patients according to clinical phenotype. In clinical practice, it would probably be necessary to have different HFpEF strategies including patients with hypertension phenotype (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, mineralocorticoid receptor antagonists, diuretics), those with LVEF below 57% (ARNI), or those with obesity (mineralocorticoid receptor antagonists). Sacubitril/valsartan seems to also be effective in patients early after HF hospitalization (mainly in the first 3 months). There is no doubt that the renal function, blood pressure, and level of potassium are important in therapy with sacubitril/valsartan. According to the product characteristic, sacubitril/valsartan is not indicated in patients with estimated glomerular filtration rate below 30 ml/min/1.73 m^2, potassium levels greater than 5.4 mmol/l, and systolic blood pressure below 100 mm Hg. In those with frailty, low blood pressure, and chronic kidneys disease, the possibility to use sacubitril/valsartan seems to be limited and closer surveillance will be necessary. All these issues will be of importance for clinicians in the future practice with sacubitril/valsartan. Finally, the described post hoc and nonprespecified analyses should be considered the hypothesis-generating studies with sacubitril/valsartan in HFpEF.

Limitations The present paper did not discuss all prior trials in HFpEF and the promising potential therapeutic methods with new molecules including soluble guanylate cyclase activators/stimulators, inhibitors of sodium-glucose transporter-2, iron or micro RNA (targeting cardiac fibrosis), and also devices for autonomic regulation with the stimulation of the vagus nerve, transcatheter interatrial shunt, or cardiac contractility modulation.

Conclusions Sacubitril/valsartan therapy in HFpEF, compared with valsartan alone, contributes to different outcomes regarding LVEF, and diverse treatment benefits, particularly in women and in symptomatic patients with slightly reduced ejection fraction. The results of the PARAGON-HF trial revealed that patients with HFpEF with some clinical profiles, for whom no evidence-based therapy is available, may benefit from treatment with sacubitril/valsartan. However, the relevance of ARNI in HFpEF still has not been clarified. Thus, more analyses and studies are required in order to better understand this heterogeneous population.

ARTICLE INFORMATION

CONFLICT OF INTEREST ML received consultation and lecture fees from Novartis and was the National Leader and Primary Investigator in the PARAGON-HF trial. The study did not receive any financial funding.

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