Review Article

Heart Failure with Preserved Ejection Fraction (HFpEF): Part 1 Review of Experience and Evidence in PARAGON-HF with Commentary

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) also known as diastolic heart failure is a complex entity. It is due to a variety of causes and has heterogeneous presentations and, therefore, has evaded evidence that is compelling for developing standard guidelines for therapeutic intervention. In February 2021, the US Federal Drug Agency approved Sacubitril-Valsartan (angiotensin receptor neprilysin inhibitor-angiotensin receptor blocker: ARNI-ARB) combination for HFpEF. The present review outlines the current experience and management of HFpEF. It also focuses on the evidence in the PARAGON-HF trial and provides a commentary. The second part of the review shall discuss the emerging importance of SGLT2 inhibitors for HFpEF.

Keywords: Cardiovascular clinical trials, Heart failure, HFpEF, Heart failure with preserved ejection fraction, PARAGON-HF, Sacubitril-Valsartan.

INTRODUCTION

The clinical syndrome of heart failure with preserved ejection fraction (HFpEF) is recognized in ICD-10 as a definitive entity. Phylogenetically, any individual with current or prior symptoms of heart failure (HF), left ventricular ejection fraction (LVEF) ≥50%, and raised heart failure biomarkers qualifies for this phenotype.[1]

Community based studies suggest that 30 to 50% patients with HF have predominant HFpEF.[2] In the Framingham Heart Study (FHS), the prevalence ranged from 8 to 66/1000 in men and 8 to 79/1000 in women among those aged 50 to 89 years.[3] While the prevalence rate for HFpEF is established, conflicting evidence exists regarding whether there is greater mortality in patients with preserved versus reduced ejection fraction (EF) heart failure. Evidence suggests that greater mortality with HFpEF in the present era is a reflection of reduced mortality in heart failure with reduced ejection fraction (HFrEF).[4,5] This is due to better response to the management of HFrEF with medicines and devices.[4,5] In past decades, HFpEF was essentially a diagnosis of exclusion and doubts had been raised regarding patients enrolled in studies that evaluated HFpEF. A review of clinical trials involving Digitalis, Candesartan, and Irbesartan with different demographic variables (elderly age, female gender, hypertension, obesity, diabetes, angina pectoris, left ventricular hypertrophy, atrial fibrillation, and chronic kidney disease and other risk factors) suggests a certain uniqueness of the HFpEF phenotype [6,7], prompting a need for more research to better understand this syndrome.[6]

Heart failure with preserved ejection fraction or diastolic heart failure occurs when the left ventricle is not able to relax properly during the diastolic (filling) phase. The amount of blood pumped is therefore sub-optimal. The pathophysiological differences between HFpEF and HFrEF syndromes are: HFpEF is commonly preceded by comorbidities mentioned above[6,7], whereas HFrEF is often associated or preceded with a loss of cardiomyocytes due to ischemia, myocarditis, valvular disorders, and genetic mutations. These differences suggest the possibility of different molecular mechanisms.[8] Literature on the cellular and molecular difference between HFpEF and HFrEF suggests that the differences in cardiac remodeling; cluster of non-cardiac comorbidities of HFpEF; coupled with low grade cardiac inflammation characterizes HFpEF.[8] Though inflammation may be common in both syndromes, the endothelial dysfunction as a result of inflammation often precedes HFpEF but is considered a consequence of

cardiomyocyte loss in HFrEF.[8] This endothelial dysfunction is due to reduced Ca^{2+} signaling and titin modification that results in ventricular stiffness and is associated in HFpEF with incre-ased perivascular and interstitial fibrosis. In contrast, in HFrEF, titin switching is less consistent and ventricular stiffness may be unaffected, increased, or even reduced.[8] Besides symptoms and signs of HF, key diagnostic criteria of HFpEF include LVEF ≥50% and elevated natriuretic peptides with or without myo-cardial abnormalities on echocardiography. All these signals are evidence of increased intravascular volume load and correspond to elevated left ventricular filling pressures and elevated pulmonary capillary wedge pressures (≥15 mmHg at rest and ≥25 mmHg on exercise).

The echocardiographic approach remains the cornerstone for HFpEF diagnosis. Echocardiographic parameters and diastolic stress tests provide several useful parameters that correlate well with indexes obtained by cardiac catheterization. The key diagnostic criteria from the current guidelines are summarized in table 1.

While the concept of HFpEF is complex and evolving, and as better treatments for HFrEF reduce short and long-term mortality, increasing diagnostic cognizance presents an unmet medical need. This is important as these patients demonstrate greater symptoms, reduced exercise capacity, impaired quality of life, with repeated hospitalizations, and higher mortality than HFrEF. Limitations of guidelines for treatment of HFpEF have prompted development of diagnostic algorithms [12,13] on a score based on various clinical variables. Table 2 summarizes these scoring systems. A higher area under the curve (0.17; 95% confidence interval (CI) of 0.12-0.22) in HFpEF shows that a higher EF is significantly associated with events while a score ≥5 is useful for the diagnosis of HFpEF.[12-14]

PHARMACEUTICAL INTERVENTIONS

Better insights in the diagnosis of HFpEF and greater understanding of mechanisms at cellular and molecular level are aiding the development of pharmaceutical medicinal products for its treatment. However, recent drug development has been preceded with many investigational medicines that failed to improve prognosis. It could be argued that the selection of patients in various randomized controlled trials may not have been optimal. Table 3 provides a brief description of the studies in HFpEF, table 4 summarizes the key characteristics of subjects enrolled in various studies, and table 5 summarizes the various outcomes of all-cause mortality, cardiovascular cause mortality, and heart failure hospitalizations from a 2018 meta-analysis of key clinical studies.[15] These studies have generated disparate evidence and have failed to change the treatment paradigm or influence development of practice guidelines. The authors of meta-analysis[15] conclude "In trials enrolling patients with HFpEF, defined using an LV ejection fraction ≥40%, beta-blockers reduce all-cause and cardiovascular mortality by 22% and 25%, respectively. The effect of treatments on functional and quality of life outcomes was limited."

LCZ696

Pharmacology: LCZ696 inhibits neprilysin and blocks

Table 1: Diagnostic criteria for HFpEF in international practice guidelines

Clinical symptoms and signs of HF	Guidelines		
	ACCF/AHA (2013)[9]	ESC (2016)[10]	CCS (2017)[11]
LV ejection fraction	>50%	>50%	>50%
Biomarkers		BNP >35 pg/mL or NT-proBNP >125 pg/mL	BNP >50 pg/mL or NT-proBNP >125 pg/mL
Imaging	LV diastolic dysfunction	LV diastolic dysfunction LA volume index > 34 mL/m^2 LV mass index (men/women) >115/95 g/m^2 E/e' >13 Mean e' <9 cm/sec LV hypertrophy and/or LA enlargement	LV diastolic dysfunction

BNP (brain natriuretic peptide); HF (heart failure); NT-proBNP (n-terminal pro-BNP); LV (left ventricle); LA (left atrium)

Table 2: HFpEF diagnostic criteria

H2FpEF (heavy, hypertension, atrial fibrillation, pulmonary hypertension, elder, filling pressure)[12]		HFA-PEFF Score[13]			
Variable	**Points**	**Major**	**Points**	**Minor**	**Points**
Heavy- Body mass index (BMI) >30 kg/m^2	2	Septal e' < 7 cm/sec or lateral e' < 10 cm/sec or averaged E/e' ≥ 15 or TR Vmax > 2.8 m/sec (PASP > 35 mmHg)	2	Averaged E/e' 9-14 or GLS < 16%	1
Hypertension- Anti-hypertensive medication >2	1	LAVI > 34 mL/m^2 or LVMI ≥ 149/122 g/m^2 (M/W) ± RWT > 0.42	2	LAVI 29-34 mL/m^2 or LVMI ≥ 115/95 m^2 (M/W) or RWT > 0.42 or LV wall thickness ≥ 12 mm	1
Atrial fibrillation (paroxysmal or persistent	3	NT-proBNP> 220 pg/mL or BNP > 80 pg/mL	2	NT-proBNP> 660 pg/mL or BNP > 240 pg/mL	1
Pulmonary hypertension -[Doppler estimate of pulmonary arterial systolic pressure (PASP) >35 mmHg]	1	NT-proBNP 125-220 pg/mL or BNP 35-80 pg/mL	2	NT-proBNP 365-660 pg/mL or BNP 105-240 pg/mL	1
Elder (>60 years)	1				
Filling pressure (E/e' >9)	1				
Total	0-9		0-8		0-4

angiotensin II type-1 receptors with Valsartan. The inhibition of neprilysin prevents any neprilysin dependent proteolytic degradation of natriuretic peptide (NP), which has vasodilatory, natriuretic, diuretic properties, inhibits renin-aldosterone release, reduces sympathetic activity causing increase in renal blood flow and increase in glomerular filtration, and has antihypertrophic and antifibrotic effects.[38] Following oral absorption, LCZ696 dissociates into Sacubitril and Valsartan. The bioavailability of Sacubitril is higher than the bioavailability of valsartan alone. Valsartan does not undergo metabolism while Sacubitril metabolizes to its active moiety LBQ657; which does not undergo further metabolism to other metabolites.[38] Both Sacubitril and Valsartan are bound by plasma proteins (94-97%) and 58-68% of Sacubitril is excreted in urine (LBQ657) and remaining in feces. Excretion of Valsartan in urine is 13% whilst 83% is eliminated in the feces.[38]

There is no significant impact due to age or gender and steady state pharmacokinetics of both ingredients are similar in subjects with renal dysfunction. Renal impairment does increase the steady state exposure of LBQ567 when compared to healthy subjects and due to their protein binding both Sacubitril and Valsartan are unlikely to be eliminated via dialysis.[38] The exposure to both Sacubitril and Valsartan increases with hepatic impairment relative to healthy volunteers.[38] Only a very minimal CYP450 enzyme mediated metabolism occurs and hence impact of medicines and food affecting CYP 450 enzymes are not expected to impact LCZ696.[38] Elevated bradykinin activity is a known mechanism of ACEI induced angioedema and as neprilysin also degrades bradykinin, concomitant administration of ACEI or within 36 hours of switching from ACEI and Sacubitril is contraindicated.[38]

Dosing: For patients currently not on ACEI or ARB, the recommended starting dose is 50 mg (Sacubitril 24 mg, Valsartan 26 mg) twice daily. This is also the dose recommended in subjects with severe renal and moderate hepatic dysfunction, which is based on the pharmacokinetic assessments of the fixed dose combination.[38] Gradual up titration can be cautiously done every 2-4 weeks to a target maintenance dose of 200 mg (97 mg/103 mg) twice daily.[38] Since pharmacokinetic data were only collected in 7% of the subjects; the dose/exposure response analysis of phase 3 trials is not feasible.[38]

Table 3: Key studies in HFpEF or diastolic heart failure

Pathways	Comments
Renin angiotensin pathway	Improvement in hypertension, reduction in hypertrophy, fibrosis, and correction of fluid imbalance, and successes in HFrEF by RAAS pathway modulations was a logical step to demonstrate improvement in HFpEF and its prognosis. Yet clinical trials failed to compile robust evidence by these therapies similar to that in HFrEF trials. Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF)[16]; angiotensin receptor blockers (Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) are trials in HFpEF.[17]
	PEP-CHF study[16] was underpowered for its primary composite end point of all-cause mortality and unplanned HF-related hospitalization, but did see some improvements in symptoms, exercise capacity, and fewer HF hospitalizations in the first observation year. In the Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial[18] compared Candesartan and placebo in HFpEF and demonstrated that subjects receiving the medicine candesartan had fewer HFH, but no mortality benefit.
MRA pathway	Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction (RAAM-PEF)[19], aldosterone antagonists (Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients with Heart Failure with Preserved Ejection Fraction (ALDO-DHF)[20], and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)[21] are some examples of failed or neutral trails in this arena.
	ALDO-DHF study[20] study with an aldosterone antagonist in HFpEF demonstrated some improvement of diastolic function and exercise capacity (the primary endpoint) but maximal exercise capacity, clinical symptoms, and quality of life were not changed; which can be a selection bias as subjects had early-stage HFpEF and without signs of volume overload.
	TOPCAT study[21] did not meet its primary composite endpoint (cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF) but demonstrated small (borderline significant) decline in hospitalizations. Interestingly, geographical differences were noted in Eastern Europe and United States sites as the criteria used for eligibility in Eastern European was based on HF hospitalization criteria (had a lower rate in placebo arm), and in the United States where eligibility was based on natriuretic peptide level had a higher event rate and spironolactone showed improvement.
Beta adrenergic pathway	Improvement in diastolic filling demonstrated some definite improvement; in HFrEF especially in elderly but were unable to garner a similar benefit in the HFpEF syndrome. The studies included, Randomized trial to determine the effect of Nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)[22]; Japanese Diastolic Heart Failure (J-DHF[23]; and Effects of Nebivolol on Clinical Symptoms, Exercise Capacity, and Left ventricular Function in Diastolic Dysfunction (ELANDD).[24]
Phosphodiesterase pathway	Preclinical research demonstrated promising results in mice, and canine HF models and in subjects with pulmonary hypertension with HFrEF and HFpEF is single center studies.[25-33] PDE5A hydrolyzes cGMP primarily generated by NO-sGC by blocking the enzyme, drugs such as Sildenafil can augment cGMP and thus PKG activity in multiple organs relevant to HF.[34] This new concept that by blocking PDE5A, cGMP/PKG signaling in HFpEF might be enhanced, with associated benefits; effect of Phosphodiesterase 5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) trial was tested; but, reported no benefit of Sildenafil compared with placebo in the primary endpoint (change in peak VO2 after 24 weeks of therapy) or in any of the secondary endpoints.[34] It is hypothesized that exercise capacity as the end point was problematic because noncardiac comorbidities could influence the outcome of HFpEF. Scientists also argued that because of low myocardial cGMP in HFpEF; cGMP modification or increase was not possible from PDE5a inhibition. In addition, the peptide levels were mild to minimally elevated in subjects in RELAX trial.[35]
Digitalis	Over centuries of use of digitalis glycoside in systolic HF, the use in diastolic HF was evaluated in subjects with a median LVEF of 52% in the Digitalis Investigation Group (DIG) trial.[36] No effect on all-cause, or cause-specific mortality, or all-cause or cardiovascular hospitalization was demonstrable; though a trend towards reduction in hospitalizations due to worsening heart failure and a trend towards an increase in hospitalizations for unstable angina was observed. This trend in unstable angina was hypothesized to be a not so well studied effect of digoxin on platelet and endothelial dysfunction.[37]
Carvedilol	Though the Japanese Diastolic Heart Failure (J-DHF) study[23] utilized the known mechanistic pharmacology of Carvedilol; this study is specifically mentioned for its geographic importance and a median prescribed dosing of 7.5 mg/day (targeted 20 mg/d). In 58 subjects (out of 125 randomized to the beta blocker group); the composite endpoint of cardiovascular death and unplanned hospitalization for any cardiovascular causes was significantly less than when compared with those administered <7.5 mg/d. For the whole study the primary outcome was a composite of cardiovascular death and unplanned hospitalization for heart failure. The authors concluded "Carvedilol did not improve prognosis of HFpEF patients overall; however, the standard dose, not the low dose, prescription might be effective. This may facilitate further investigation."

Table 4: Comparative characteristics of the previous studies in HFpEF

Trials	Investigational Product	Inclusion LVEF (%)	Concomitant Meds
PEP-CHF[16]	Perindopril	>50	Diuretics, BB, CCB, Nitrate, antiplatelet, hypolipidemic, hypoglycemic
RAAM-PEF[19]	Eplerenone	>50	Diuretics, ACEI, ARB, BB,
I-PRESERVE[17]	Irbesartan	>45	Diuretics, ACEI, BB. Digitalis, ARA, Statins
ALDO-DHF[20]	Spironolactone	>50	Diuretics, ACEI, BB, Statins
TOPCAT[21]	Spironolactone	>45	Diuretics, ACEI, ARB, BB, Statins
CHARM -P[18]	Candesartan	>40	Diuretic, ACEI, BB, ARA, Digitalis, Others
SENIORS[22]	Nebivolol	33-34	Diuretics, ACEI, ARB, Digitalis, CCBs, Antiplatelets, Statins
ELANDD[24]	Nebivolol	>45	Diuretics, ACEI, Statins
RELAX[34]	Sildenafil	>50	Diuretics, ACEI, ARB, BB, ARA, Statins
DIG[35]	Digitalis	>45	Digitalis
J-DHF[23]	Carvedilol	>40	Diuretics, ACEI, ARB, Digitalis, ARA

BB: beta blockers; CCB: calcium channel blockers; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers.

Table 5: Summary of endpoints in trials for HFpEF (Adapted from Ref 15)

		Drug class			Follow-up		Entry LVEF	
	All trials	BB	RAAS antagonists	Others	<12 months	>12 months	40-49%	>50%
All-cause mortality	0.96	0.78 (p=0.008)	1.00	0.95	0.79 (p=0.01)	0.99	0.96	0.99
CV Mortality	0.95	0.75 (p=0.01)	0.99	1.01	0.71 (p=0.005)	0.99	0.95	
HFH*	0.88 (p=0.002)	0.67	0.90 (p=0.01)	0.81	0.67 (p=0.02)	0.90 (p=0.02)	0.88 (p=0.002)	0.51

p value < 0.05, significant; * HFH: Hospitalization for heart failure

Safety: Considering the novelty of the fixed dose combination both short-term and long-term safety warrant consideration. The special adverse events of interest are angioedema, hypotension, hyperkalemia,worsening renal function, and effect on cognition. A recent pooled meta-analysis[39] demonstrates a numerical higher risk of symptomatic hypotension (RR 1.47, 95% CI 1.34-1.60, p = 0.0001); reduction in renal function (RR 0.81, 95% CI 0.74-0.94, p = 0.005); no significant difference in hyperkalemia (RR 0.97, 95% CI 0, 86 1.11, p = 0.70); significantly lower serious hyperkalemia (> 6.0 mmol/L) (RR = 0.76, 95% CI [0.65, 0.89], p = 0.00007); and no significant difference in angioedema (RR = 1.42, 95% CI 0.52, 3.87, p = 0.49). Worsening of renal function was defined as decrease in eGFR ≥ 35% or increase in serum creatinine ≥0.5 mg/dL from baseline and decrease in eGFR ≥ 25% or increase in serum creatinine >2.5 mg/dL. Hyperkalemia was defined as serum potassium >5.5 mmol/L and serious hyperkalemia was defined as > 6.0 mmol/L in this meta-analysis.

Since neprilysin is a beta amyloid-degrading enzyme in the brain, there is a theoretical risk that inhibition of neprilysin could accentuate beta amyloid deposits in the brain increasing the risk of Alzheimer's disease. Analysis of adverse event data from a phase 3 trial did not reveal a cognitive impairment signal[40], and that cognitive impairment differed numerically but not substantively between the combination of Sacubitril and Valsartan, and Valsartan only.[40]

Efficacy in HFpEF: In the meta-analysis[39] that included the PARAGON-HF trial in HFpEF, there were no significant differences in all-cause mortality and cardiovascular mortality between the Sacubitril-Valsartan group and the control group. The analysis of data demonstrated that the use of Sacubitril-Valsartan had a similar benefit in reducing the composite risk of hospitalization for HF in patients with HFrEF compared to subjects with HFpEF.

Paragon-HF trial: Briefly, the baseline characteristics in the two groups were balanced except for numerical increase in subjects receiving mineralocorticoid-receptor antagonists (MRA) in the valsartan group (Table 6). The follow-up period for the study was 30-41 months (median 35 months). The study population included subjects with factors of risk for HFpEF. Participants had LVEF >50%; with more belonging to NYHA class I and II and history of hospitalizations for heart failure with a moderately increased NT-proBNP. Target dose was 200 mg (97 mg of Sacubitril with 103 mg of Valsartan) twice daily, or 160 mg twice daily of Valsartan. Evaluation was done every 4 to 16 weeks. The doses of the medicines could be titrated down if the target dose led to unacceptable side effects. Renin angiotensin system inhibitors other than mineralocorticoid-receptor antagonists were discontinued before the run-in period, but all other background medications were continued.

The primary outcome was a composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes and the study had a 95% power to detect a 22% difference (lower in Sacubitril-Valsartan group) between the group (30% lower risk for HFH and 10% for CV deaths) requiring 1847 events with first-primary event rate of 9/100 patient-years. Table 7 below summarizes the various outcomes of this study.

The results of the analysis show numerically few (not statistically significant) primary endpoint events in the Sacubitril-Valsartan group, but an overall 13% (RR 0.87 (95% CI 0.75-1.01) reduction in relative risk was observed with the CI crossing the line of unity by 0.01.[41] The trend in the HFH was 15% reduction and 5% reduction in death from any-cause (both not statistically significant). Furthermore, prespecified secondary outcomes (the change in the NYHA class from baseline to month 8 and decline in renal function) favored SacubitrilValsartan over Valsartan.

The authors postulated that the population with HFpEF are phenotypically heterogenous and so that data raises the possibility of a differential effect; especially in subjects with LVEF between 45 to 57% and in women who usually comprise majority of the subjects with HFpEF. In the 12 prespecified subgroups, results suggest benefit with Sacubitril combination over valsartan alone. Table 8 illustrates this further.

COMMENTARY

Given these results and experience with studies in HFpEF, it could be argued that the jury is still out. Alternatively, the results can be put in context of the burden of illness and a select group of patients (Caucasians, females, with LVEF between 40 to 60% with atrial fibrillation and estimated GFR <60 ml/min/1.73^2, moderately high NT-proBNP and not able to take ACE-I). This would mean that the results should be used as evidence for targeted treatment. Physicians could wait for a Cochrane meta-analysis in patients with HFpEF or wait for confirmatory evidence

Table 6: Key baseline characteristics of the PARAGON-HF trial[41]

Characteristics	Sacubitril-Valsartan n = 2,407	Valsartan n = 2,389
Age (years, mean)	72.7	72.8
Females, n (%)	1,241 (51.6)	1,238 (51.8)
Systolic BP (mmHg)	130.5 ± 15.6	130.6 ± 15.3
Body mass index (kg/m^2)	30.2 ± 4.9	30.3 ± 5.1
Estimated GFR (ml/min/1.73m2)	63 ± 19	62 ± 19
LVEF (%)	57.6 ± 7.8	57.5 ± 8.0
NT-proBNP (pg/ml), Median (IQR)	904 (475-1,596)	915 (453-1,625)
NYHA I, n (%)	73 (3.0)	64 (2.7)
NYHA II, n (%)	1,866 (77.5)	1,840 (77.0)
NYHA III, n (%)	458 (19.0)	474 (19.8)
NYHA IV or missing, n (%)	10 (0.4)	11 (0.3)
HFH, n (%)	1,135 (47.2)	1,171 (49.0)
Diuretics at randomization, n (%)	2,294 (95.3)	2,291 (95.9)
ACEI or ARB at screening, n (%)	2,074 (86.2)	2,065 (86.4)
MRA at randomization, n (%)	592 (24.6)	647 (27.1)
Beta blocker at randomization, n (%)	1,922 (79.9)	1,899 (79.5)

Table 7: Outcomes of HFpEF in the PARAGON-HF Trial[42]

Outcome	Sacubitril-Valsartan, n = 2,407	Risk, 95% CI	Valsartan, n = 2,389
Primary composite outcome*	894	RR = 0.87, [0.75, 1.01]	1,009
Total no. of HFH	690	RR = 0.85, [0.72, 1.00]	797
Death from CV causes	204	HR = 0.95, [0.79, 1.16]	212
Secondary outcomes			
Death from any cause	342	HR = 0.97, [0.84-1.13]	349
Renal composite outcome	33	HR = 0.50, [0.33-0.77] OR = 1.45, [1.13-1.86]	64
Δ NYHA score at 8 months, n/total n (%)			
Improved	347/2,316 (15%)		289/2,302 (12.6%)
Unchanged	1,767/2,316 (8.7%)		1,792/2,302 (77.8%)
Worsened	2,020 /2,316 (8.7%)		221/2,302 (9.6%)

* = total hospitalizations for heart failure and death from cardiovascular causes.

Table 8: Key subgroup results

Subgroup	# Events / # Patients	Ratio	95% CI
Age ≥ 65	1627/3971	0.85	0.73, 0.99
Age < 75	938/2597	0.82	0.66, 1.02
Females	923/2479	0.73	0.59, 0.90
Race-White	1542/3907	0.83	0.71, 0.97
No history of diabetes	862/2301	0.84	0.68, 1.04
History of diabetes	1041/2069	0.89	0,74, 1.09
SBP ≤ 137 mm Hg, median	984/2450	0.88	0.72, 1.07
SBP > 137 mm Hg, median	919/2344	0.86	0.89, 1.06
Atrial fibrillation present	1140/2521	0.83	0.69, 1.00
Estimated GFR < 60 mL/min/1.732	1115/2342	0.79	0.66, 0.95
NYHA Class I or II	1402/3843	0.90	0.90, 1.06
NYHA class III or IV	499/951	0.79	0.59, 1.06
LVEF median < 57	1048/2495	0.78	0.64, 0.95
LVEF median >57	855/2301	1.00	0.81, 1.23
NT-proBNP ≤ 911 pg/mL, median	708/2309	0.85	0.85, 1.08
NT-proBNP> 911 pg/mL, median	1183/2378	0.87	0.73, 1.05
Able to take ACE1	1817/4534	0.87	0.75, 1.01

from another trial in population with LVEF between 40-60% or the guidelines may need revision to include subcategories of HFpEF (EF >60%); HFrEF (EF <40%); and HFmEF (EF between 40-60%) as defined by the Canadian Cardiovascular Society.[11]

Admittedly, the result of PARAGON-HF data alone may not cross the benchmark for incorporation into the guidelines; but if the studies on HFrEF and HFpEF are taken together, it can be surmised with some confidence that the trend with Sacubitril-Valsartan studies can be expected to have benefits in this population between 10-15%; or perhaps it could be speculated that the effect could have been more had the comparator arm was a placebo (which is ethically not possible in this population study).

Given the above considerations and awaiting the discovery of the "holy grail" for this population from additional research and/or analysis of data; what can the good doctor do?

One answer could be a targeted treatment approach which can be further refined with application of evolving risk calculators or algorithms (briefly narrated below) for both diagnostic and prognostic estimations in this disease area. The ARIC HFpEF risk calculator[42] is designed for black

and white adults >55 years of age with HFpEF (EF >50%) admitted to the hospital with acute decompensation and prediction of 28 days and 1-year mortality from admission to the hospital. H2FPEF score[43] relies on 6 baseline characteristics and echocardiography variables for diagnostic discrimination at time of admission for dyspnea.

The MAAGIC algorithm[44] included 39.372 patients with HF from 30 cohort studies; with a mortality of 40.2% and a median follow-up of 2.5 years. A validation of MAGGIC done for HFpEF suggested a better calibration for hospital outcomes and provides a useful tool of risk stratification for both morbidity and mortality in HFpEF.

European Society of Cardiology[45] suggested a scoring system for diagnostic accuracy (HFA-PEFF); where a score of >5 implies definite HFpEF and a score of <1 makes HFpEF unlikely and an intermediate score (2-4) implies diagnostic uncertainty.

In our opinion, evidence with the Sacubitril-Valsartan combination in HFrEF is robust but similar robustness eludes in HFpEF. Furthermore, though preclinical safety data and cognitive scoring/analysis in heart failure trials (both HFrEFandHFpEF) with LCZ696 provide comfortable and promising confidence for short to medium term use; long term effect of suppression of neprilysin and the postulation of a role in the degradation of beta-amyloid in the brain; resulting in a theoretically increase beta-amyloid plaque deposition in the brain with a potential to increase the risk of Alzheimer's disease, cannot be refuted or confirmed at this time and awaits the results in 2022[46] of the ongoing prospective evaluation of Sacubitril-Valsartan on cognitive function in heart failure (PERSPECTIVE: NCT02884206). Whether the pandemic of COVID-19 will affect the recruitment or affect cognition with the randomized patients who get infected by COVID-19 virus; irrespective of their symptoms is also unknown.[47]

Given the above conundrum and unresolved questions and unknown value of risk calculators; it may be appropriate to consider a population where HFpEF may be pathophysiological higher and targeted treatment may be more optimal. One such population is those with diabetes mellitus (DM), hitherto not paid attention to, until recently. In DM where "diastolic dysfunction" pathogenesis of cardiac remodeling is multifactorial- from inadequate glucose metabolism to sub-clinical atherosclerotic diseases process to nonatherosclerotic microvascular damage early in the diagnosis of DM; a 2-5-fold increase in risk of HF is well known, and around 45% of patients with HF have concomitant diabetes as an underlying medical history.[48-50]

Though public health policies, guidelines, and regulatory approvals are based on the clinical trial results, clinical trials protocol development for medicines development is a complex thought process. First, the protocol must be watertight such that the intrinsic validity (research question/hypothesis and population studied are devoid of heterogeneity or confounding variables or the sample size has to be huge, so as to enable statistical differentiation between different subpopulations or various variables) or the extrinsic validity (application to the general population of any results) must be based on careful evaluation of the results and their application or customization to an individual patient; especially in diseases that have high heterogeneity.

In addition, trials could enroll fewer sick subjects (and large sample size) with guidelines mandated background therapy(ies) for comparative assessment with placebo. This is not the case for the PARAGON-HF study as comparative groups had active treatment.

Alternatively in active comparative studies, treatment difference objectives could be either to seek superiority or non-inferiority between the two active treatment groups. The gestalt may be towards superiority because a rejection of a null hypothesis with high significance gives a greater chance of "true positive" and the application of the results into the guidelines. In non -inferiority trial designs, the study designers must consider the non-inferiority margin in the sample population that represents the population at large, have less comorbidities or confounding variables, or those whose safety might be threatened by inclusion in the study.

Given the above complex nature of clinical research; scientists, researchers, and medicines developers usually tend to define the specific sample population that is targeted to optimize a favorable response to the selected endpoint. It is because of this clinical trials have demonstrated efficacy and safety in HFrEF but the same has been a Herculean task in HFpEF for regulatory approval; until the approval based on PARAGON-HF study results.

It remains to be seen if heart failure societies and academicians would incorporate it into guidelines and what position payers would take for utilization of the combination for HFpEF. Perhaps a more interesting trial could be to compare 2 active treatments in patients with ejection fraction between 40 to 60% and with NYHA class II or above but on most optimized background therapy with a

non-inferiority margin of 15%; something like the VALIANT study.[51]

Recently meta-analysis of cardiovascular outcomes with sodium glucose cotransporter-2 (SGLT-2) inhibitors has reported a reduced rate of major adverse cardiac events (MACE). This will be the subject of discussion in part II of this mini-series.

CONCLUSION

Heart Failure is a complex condition and HFpEF has its hurdles in diagnosis and treatment; but the burden of illness on lost working life capacity and early mortality is an unmet medical need.

Sacubitril-Valsartan combination trial (PRAGON-HF) demonstrated a numerical trend in benefit without statistical significance. Thus, considerations for a universal and wide ranging use for the use of medicines remain elusive but can be considered on a case by case basis or per physicians specialized experience/expertise in managing these complex syndromes.

Trial design and relevance of its application to population at large is even more complex and requires experienced researchers with seasoned thinking who can balance the data that drives the endpoint and the generalization into the larger population that is simpler to implement but is unquestionable. A tall order can be done and would require deep pockets with large sample size or a population based real world evidence-informed-practice based design. Beyond therapeutics, the COVID-19 pandemic has profoundly changed clinical care and research including the performance and confounding analysis of COVID-19 and COVID-19 long term effects on cardiac myocytes and cardiovascular drug development. New principles need to be developed, tested, and incorporated into contingency planning for future public health medicines development and potential disruptions, including the potential long-term effects of COVID-19.

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