JOURNAL REVIEW

New England Journal of Medicine (NEJM)
Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction (**PARAGON Trial)**

Solomon SD, Mcmurray JJ, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine. 2019;381(17):1609-1620. doi:10.1056/nejmoa1908655.

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Background

What is Ejection Fraction (EF)/Normal EF/Low EF/High EF?

- Ejection fraction (EF) is a measurement of how much blood the left ventricle pumps out with each contraction. Normal EF is between 50 – 70 %, Low EF is < 40% (HF/Cardiomyopathy) and High EF is > 75% (Hypertrophic Cardiomyopathy).
- An ejection fraction measurement higher than 75 percent may indicate a heart condition such as hypertrophic cardiomyopathy

What is Preserved Ejection Fraction (HFpEF) vs Reduced Ejection Fraction (HFrEF)?

- HFpEF is EF of > 50% (Impaired ventricular relaxation and filling during diastole) vs HFrEF is EF < 40% (Impaired ability to eject blood during systole)

What is the Mechanism of Action of Entresto (ARNI)?

- Entresto is a combination of a Neprilysin inhibitor (Sacubitril) and an ARB (Valsartan). Neprilysin is the enzyme responsible for degradation of several beneficial vasodilatorv peptides, including natriuretic peptides, adrenomedullin substance p and bradykinin. These peptides counteract the effects of RAAS activation and produce vasodilation.
- Indication: NYHA Class II-IV patients to reduce HF hospitalizations and cardiovascular death. Entresto is usually added to other HF therapies (BB's/Loops) in place of an ACEI/ARB.

Current Treatment for HFpEF [2017 ACC-AHA Guidelines]

- In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension.
- The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. [II A]
- In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5 mEq/L) → Aldosterone Receptor Antagonists might be considered to decrease hospitalizations [II B]

Clinical Trials on Entresto

- The FDA approval of Entresto was based on results from a randomized, double-blind, Phase III clinical trial known as **Paradigm-HF**, which was conducted to determine the safety and efficacy of the drug.
- **Paradigm-HF** enrolled 8,442 patients with reduced ejection fraction (HFrEF) and NYHA Class II-IV heart failure. The study compared Entresto with another ACE inhibitor, Enalapril and was designed to find out whether it is superior to Enalapril in decreasing cardiovascular mortality by at least 15%

There were a handful of previous clinical trials for treatment of HFpEF such as:

Trial	Comparison	Population	Duration	Results
CHARM	Candesartan vs Placebo	3,023 patients with NYHA class II to IV HF, LVEF > 40%, and prior hospital admission for cardiac reason	36 months	No difference between groups in CV mortality; CV, HF, or all-cause hospitalization
J-DHF	Carvedilol vs Placebo	245 patients with HF and EF > 40%	3.2 years	No difference between groups in CV or HF hospitalization

Purpose & Objective	The purpose of this study is to evaluate the effect of Entresto compared to valsartan in the reduction of cardiovascular death and heart failure (HF) hospitalizations in patients with HFpEF

Methods

Study Design	Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled

Inclusion Criteria

- Left ventricular ejection fraction (LVEF) ≥45% during screening or within 6 months prior to study entry.
- Symptom(s) of heart failure (HF) and requiring treatment with diuretic(s) for HF at least 30 days prior to study entry.
- Current symptom(s) of HF
- Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram.
- Elevated NT-proBNP

Exclusion Criteria

- Any prior measurement of LVEF < 40%.
- Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months, or urgent PCI within 3 months or an elective PCI within 30 days prior to entry.
- Any clinical event within the 6 months prior to entry could have reduced the LVEF (e.g., MI, CABG), unless an echo measurement performed after the event confirms a LVEF ≥45%.
- Current acute decompensated HF requiring therapy.
- Patients who require treatment with 2 or more of the following: an ACEI/ARB
- Alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, hemoglobin (Hgb) <10 g/dl, or BMI > 40 kg/m2.
- SBP ≥ 180 mmHg at entry, or SBP >150 mmHg and <180 mmHg at entry unless the patient is receiving 3 or more antihypertensive drugs, or SBP < 110.

Allocation

- Participants who had no unacceptable side effects in both run-in phases and whose laboratory values remained within prespecified safety criteria were randomly assigned in a 1:1 ratio to receive double-blind treatment with either sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily).
- Patients were evaluated at trial visits every 4 to 16 weeks.

Intervention(s)

Sacubitril + Valsartan [Entresto]

- Entresto was orally administered [97 mg + 103 mg] BID

Valsartan

- Valsartan will be orally administered [160 mg] BID
- Patients were evaluated at trial visits every 4 to 16 weeks

Renin–angiotensin system inhibitors other than mineralocorticoid-receptor antagonists were discontinued before the run-in period, but all other background medications were continued.
The dose of the trial drugs could be adjusted down if the target dose led to unacceptable side effects.

Endpoints

Primary Endpoint(s)

- Composite Of Total Hospitalizations For Heart Failure & Death From Cardiovascular Causes

Cardiovascular Death Examples (As Per Appendix)

- Fatal Myocardial Infarction (MI)
- Heart Failure
- Sudden Death
- Presumed Sudden Death
  - Death occurring unexpectedly in an otherwise stable subject last seen alive ≥ 24 hours previously, with circumstances suggestive of sudden death
- Presumed Cardiovascular Death
  - Death likely due to a cardiovascular cause in which the available clinical data is insufficient to support a more specific cause of death
- Fatal Stroke
- Fatal Pulmonary Embolism (PE)
- Cardiovascular Procedure Related Death
  - PCI, Coronary Artery Bypass Graft (CABG), Valvular Procedures

Non-Cardiovascular Death Examples (As Per Appendix)

- Infection, Malignancy, Pulmonary Failure, GI, Renal Failure, Trauma, Suicide

Secondary Endpoint(s)

- Change in NYHA Class from Baseline to 8 mo.
  - Improved
  - Unchanged
  - Worsened
- Change in KCCQ Clinical Summary Score at 8 mo.
- Development of End-Stage Renal Disease
- Death from Any Cause

Statistical Analysis

- The trial determined that 1847 primary events would provide the trial with 95% power to detect an overall 22% lower rate in the sacubitril–valsartan group and at least 80% power to detect an overall 19% lower rate.
- Analyses of the primary and secondary outcomes were conducted according to the intention-to-treat principle. If the primary outcome reached significance, a hierarchical, sequentially rejective procedure was planned for the analysis of secondary efficacy outcomes, with the alpha level split equally between KCCQ score and NYHA class, followed by the renal composite outcome.

Results

Enrollment

- 10,359 Patients Were Assessed For Eligibility
  - 5746 Entered Valsartan Run-In Phase
  - 5205 Entered Sacubitril-Valsartan Run-In Phase
    - 2407 – Included in Entresto Group & 2389 – Included in Valsartan Group

The median duration of follow-up was 35 months in each group.

Baseline Characteristics

Characteristic	Entresto (n=2407)	Valsartan (n=2389)
Age	72.7 +/- 8.3	72.8 +/- 8.5
Race – no. (%)	**1963 (81.6) [White]**	**1944 (81.4) [White]**
	52 (2.2) [Black]	**50 (2.1) [Black]**
	297 (12.3) [Asian]	310 (Asian)
	95 (4.0) [Other]	85 (3.6) [Other]
NYHA Class – no (%)	73 (3.0) [Class I]	64 (2.7) [Class I]
	1866 (77.5) [Class II]	**1840 (77.0) [Class II]**
	458 (19.0) [Class III]	474 (19.8) [Class III]
	8 (0.3) [Class IV]	11 (0.5) [Class IV]

	Baseline Medications (Pre-Trial)	2294 (95.3) [Diuretic Agent]	2291 (95.9) [Diuretic Agent]
		2074 (86.2) [ACEI/ARB]	2065 (86.4) [ACEI/ARB]
		592 (24.6) [MRA]	647 (27.1) [MRA]

Primary Results

Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)

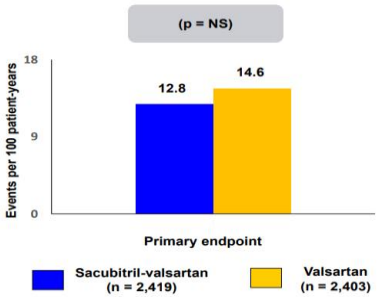
At a median follow-up of 35 months, the frequency of the primary composite outcome of total hospitalizations for HF and death from cardiovascular causes was not statistically significantly lower with sacubitril-valsartan than with valsartan (894 primary events in 526 patients in the sacubitril-valsartan group and 1009 primary event in 557 patients in the valsartan group; rate ratio 0.87; 95% CI 0.75-1.01) and there was a small, almost significant difference in rates of hospitalization for HF (rate ratio 0.85; 95% CI 0.72-1.00).

Secondary Results

Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

Rates of all-cause mortality were similar in the two groups (14.2 and 14.6 percent).

Results Summary



RESULTS

- Primary efficacy endpoint: rate of cardiovascular deaths or hospitalizations for heart failure was 12.8 events per 100 patient-years in the sacubitril-valsartan group vs. 14.6 events per 100 patient-years in the valsartan group (p = NS)
- NYHA class improvement: 15.0% in the sacubitril-valsartan group vs. 12.6% in the valsartan group (p < 0.05)

CONCLUSIONS

- Among patients with heart failure with preserved ejection fraction, sacubitril-valsartan was not effective at reducing the incidence of cardiovascular death or hospitalization for heart failure compared with valsartan

Solomon SD, et al. N Engl J Med 2019;Sep 1:[Epub]

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
Female	923/2479	0.73 (0.59–0.90)

Subgroup analysis suggested a possible benefit of sacubitril-valsartan for the primary outcome among patients with an LVEF ≤57 percent (the median) and among women.

Table 3. Adverse Events during Randomized Treatment.

Event	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	P Value
Hypotension with systolic blood pressure <100 mm Hg — no. (%)	380 (15.8)	257 (10.8)	<0.001
Elevated serum creatinine — no. (%)			
≥2.0 mg/dl	261 (10.8)	328 (13.7)	0.002
≥2.5 mg/dl	97 (4.0)	109 (4.6)	0.36
≥3.0 mg/dl	38 (1.6)	40 (1.7)	0.79
Elevated serum potassium — no./total no. (%)			
>5.5 mmol/liter	316/2386 (13.2)	361/2367 (15.3)	0.048
>6.0 mmol/liter	75/2386 (3.1)	101/2367 (4.3)	0.04
Angioedema — no. (%)	14 (0.6)	4 (0.2)	0.02
Liver-related adverse event — no. (%)	151 (6.3)	178 (7.5)	0.11
Hyperkalemia	19 (0.79)	42 (1.75)	

Patients in the sacubitril-valsartan group had higher incidences of hypotension and angioedema, and lower incidences of hyperkalemia.

Author's Conclusions	
• Among patients with HFpEF, Entresto was NOT effective at reducing the incidence of CV Death or Hospitalizations for HF compared with Valsartan • Patients receiving Entresto were more likely to have hypotension and angioedema but LESS likely to have hyperkalemia.	
Overall Critique and Discussion of Findings and Clinical Relevance	
Strengths	• Large sample size • Patients randomized evenly in a 1:1 ratio • Good baseline characteristics – External Validity not as issue as both Study Arms were equally represented
Limitations	• Internal Validity o In regards to both arms of the study for Race it was poorly represented as ~ 81% were White patients and only ~2% African American and 12% Asian o In regards to both arms of the study for NYHA Class it was poorly represented with ~ 77% Class II (these patients are relatively well managed in Class II compared to III-IV). The amount of patients should have been equally distributed throughout the Class I → IV.
Discussion	• Among patients with HFpEF, sacubitril-valsartan was not effective at reducing the incidence of cardiovascular death or hospitalization for HF compared with valsartan. • There is possible benefit for Entresto among those with EF in lower range of eligibility (45-57%) – these groups deserve further clinical studies. o Entresto was primarily made to work on patients with lower EF %. The PARAGON trial inclusion criteria only permitted patients with EF > 45%, further studies need to explore patients closer to the lower end of the inclusion criteria to get a better understanding on if Entresto is truly not useful in HFpEF by changing the lower end of the inclusion criteria to > 40%. • There was less decline in renal function among the sacubitril-valsartan group. • This trial contrasts with the PARADIGM-HF trial, which documented benefit from sacubitril-valsartan among patients with HF with reduced EF.
Your Conclusions	• At this time I believe there is no need for the addition of a Neprilysin Inhibitor such as Sacubitril • We should continue to follow ACC Guidelines for symptomatic & hypertension management • We need further studies for patients with mid-range EF (45-57%) to see if there is morbidity and mortality benefit with Entresto.

References

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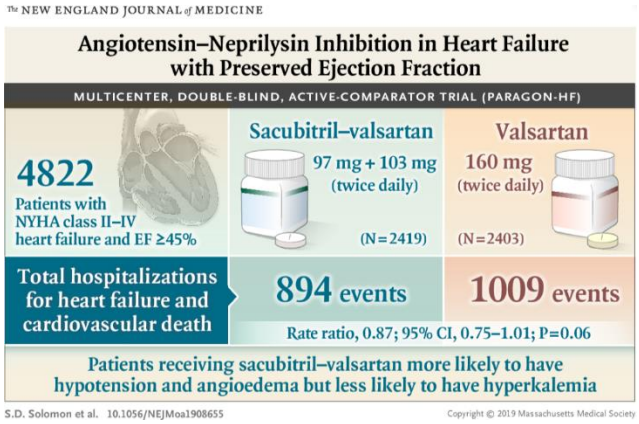
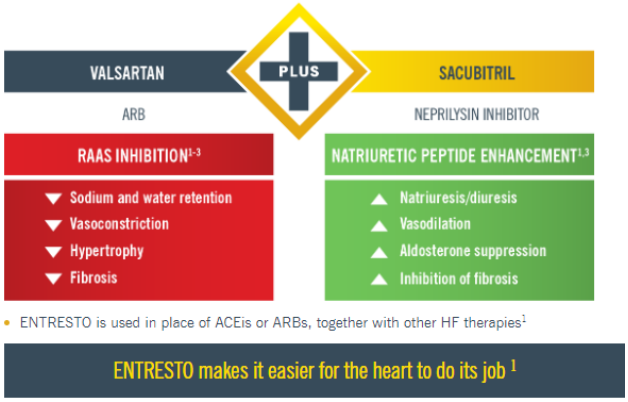


New York Heart Association (NYHA) Classifications

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity (e.g., walking , climbing stairs) does not cause symptoms of HF.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity, e.g. walking short distances (20-100 yards), causes symptoms of HF.
IV	Unable to carry on any physical activity without symptoms of HF, or, symptoms of HF at rest.



Worsening Renal Function

(50% Reduction in estimated eGFR):
This event will be defined as a sustained reduction in estimated GFR (eGFR) by 50% from baseline (Randomization, Visit 199/201) as determined by 2 consecutive post-baseline central laboratory measurements separated by ≥ 30 days. This event will be identified programmatically by the sponsor and will not be adjudicated by the CEC.

Criteria

Inclusion Criteria:

- Left ventricular ejection fraction (LVEF) ≥45% by echo during screening epoch or within 6 months prior to study entry.
- Symptom(s) of heart failure (HF) and requiring treatment with diuretic(s) for HF at least 30 days prior to study entry.
- Current symptom(s) of HF
- Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram.
- Elevated NT-proBNP

Population

Inclusion Criteria

- Age ≥18 years
- NYHA class II-IV symptoms
- LVEF ≤40% until 2010 at which point this was reduced to ≤35%
- If no HF hospitalizations in prior year: BNP ≥150 pg/mL or NT proBNP ≥600 pg/mL
- If a HF hospitalization in prior year: BNP ≥100 pg/mL or NT proBNP ≥400 pg/mL
- ACE-inhibitor or ARB therapy with stable dose for prior 4 weeks, equivalent to enalapril ≥ 10 mg/day
- Beta blocker with stable dose for prior 4 weeks