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LATEST 2023 DATA

PUBLISHED IN THE *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY*

PARAGLIDE-HF

Prospective comparison of **ARN**i with **A**RB **G**iven following stabi**L**ization **I**n **DE**compensated **HF**pEF

Learn more at EntrestoHCP.com

Start Early. Start Now. Start ENTRESTO®.

ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor.

INDICATION

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

IMPORTANT SAFETY INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue ENTRESTO as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus**

ENTRESTO is contraindicated in patients with hypersensitivity to any component. ENTRESTO is contraindicated in patients with a history of angioedema related to previous angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

ENTRESTO is contraindicated with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. ENTRESTO is contraindicated with concomitant use of aliskiren in patients with diabetes.

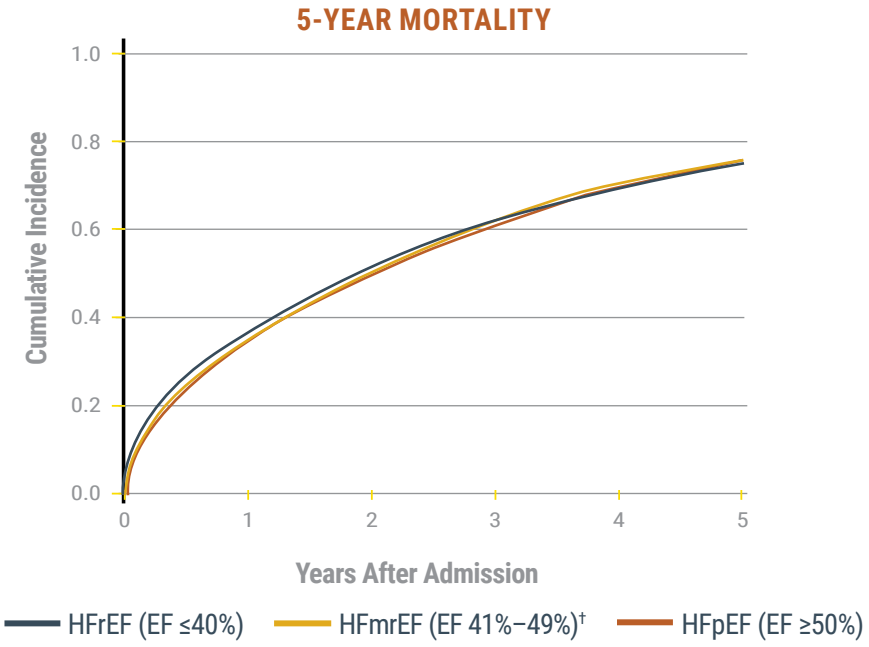
Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

UNMET NEED IN HFmrEF AND HFpEF

UNTIL RECENTLY, THERE HAS BEEN NO CLEAR HF STANDARD OF CARE TREATMENT IN HFmrEF AND HFpEF[1]

HFmrEF and HFpEF have a similar prognosis to HFrEF—**it is critical to treat these patients urgently**[1,2]

THE 5-YEAR MORTALITY RATES FOR PATIENTS WITH HFmrEF AND HFpEF ARE COMPARABLE TO HFrEF (75.7%, 75.7%, AND 75.3%, RESPECTIVELY), ACCORDING TO DATA FROM THE GET WITH THE GUIDELINES®-HF REGISTRY[2]*



- Historically, treatment of HFpEF was limited to managing patients' comorbidities[1]
- The 2023 ACC ECDP for HFpEF calls for timely implementation of GDMT in HFpEF management[1]

Ensure your HFpEF patients are on all appropriate components of GDMT[1]

IMPORTANCE OF ASSESSING NT-proBNP IN HF MANAGEMENT

ELEVATED LEVELS OF NT-proBNP HAVE BEEN ASSOCIATED WITH POOR HF OUTCOMES[3]

- A decrease in NT-proBNP of >30% from baseline has been associated with a reduced risk of CV death and HF hospitalization[4]
- The 2022 AHA/ACC/HFSA HF Guideline strongly recommends measuring BNP or NT-proBNP levels at admission in patients hospitalized for HF to establish prognosis (Class 1 recommendation)[5]

*In a study including patients with HFrEF (LVEF ≤40%), HFmrEF† (LVEF 41%–49%), and HFpEF (LVEF ≥50%) who were 65 years old and hospitalized for HF, the GWTG-HF registry was merged with claims from the US Centers for Medicare & Medicaid Services from 2005 through 2009, with 5 years of follow-up through the end of December 2014. A total of 39,982 patients from 254 hospitals who were admitted for HF were included: 18,299 (46%) had HFpEF, 3285 (8.2%) had HFmrEF,† and 18,398 (46%) had HFrEF. Overall, median survival was 2.1 years. In a risk-adjusted survival analysis, all 3 groups had a similar 5-year mortality (HFrEF 75.3% vs HFpEF 75.7%; HR 0.99 [95% CI: 0.958–1.022]; HFmrEF† 75.7% vs HFpEF 75.7%; HR 0.99 [95% CI: 0.947–1.046]).
†Defined as "HFbEF" (HF with borderline EF) in the analysis.

ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; ECDP, Expert Consensus Decision Pathway; EF, ejection fraction; GDMT, guideline-directed medical therapy; GWTG-HF, Get With The Guidelines®-Heart Failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFSA, Heart Failure Society of America; HR, hazard ratio; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

IMPORTANT SAFETY INFORMATION (cont)

Angioedema: ENTRESTO® may cause angioedema. Angioedema associated with laryngeal edema may be fatal. ENTRESTO has been associated with a higher rate of angioedema in Black patients and in patients with a prior history of angioedema. ENTRESTO should not be used in patients with hereditary angioedema. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered.

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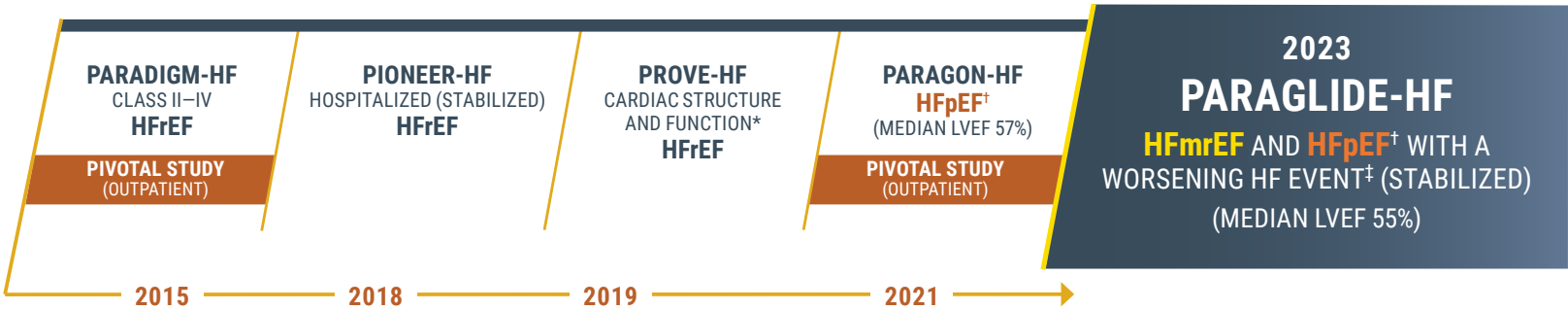
ENTRESTO® is prescribed across the spectrum of patients from HFrEF to HFpEF with LVEF ≤60%, now featuring the latest data from **PARAGLIDE-HF**[6]

AS THE FIRST AND ONLY ARNi, ENTRESTO HAS PAVED THE WAY IN PATIENTS WITH LVEF ≤60%[6-12]:



2022 AHA/ACC/HFSA HF Guideline strongly recommends ENTRESTO for HFrEF and has expanded its recognition in select HFmrEF and HFpEF patients with LVEF on the lower end of the spectrum[5§]

~80% of patients with HF have LVEF ≤60% and may be appropriate for ENTRESTO[7]

The 2023 ACC ECDP for HFpEF favors the use of ENTRESTO instead of an ARB for HFpEF patients with LVEF <55% to 60%, unless not feasible due to contraindication, cost, or intolerance[1]

IN PARAGON-HF: ENTRESTO REDUCED TOTAL HF HOSPITALIZATIONS

PARAGON-HF study design: PARAGON-HF was a randomized, double-blind, active-controlled trial comparing ENTRESTO to valsartan in 4796 adult patients with symptomatic (NYHA Class II–IV) HFpEF (LVEF ≥45%, elevated levels of natriuretic peptides, and structural heart disease). After completing the run-in period with valsartan, followed by ENTRESTO, patients entered the double-blind period and were randomly assigned (1:1) to ENTRESTO 97/103 mg BID (n=2407) or valsartan 160 mg BID (n=2389). The median follow-up duration was 35 months, and patients were treated for up to 4.7 years.[6,11]

ENTRESTO reduced total HF hospitalizations and CV death in a prespecified subgroup analysis of PARAGON-HF patients with LVEF at or below the median (57%)[6,13†]:

22% **RELATIVE RATE REDUCTION**
in composite end point vs valsartan RR 0.78 (95% CI: 0.64–0.95); 3.6% ARR[‖]
Driven by reduction in HF hospitalizations

At the primary end point, a composite of total (first and recurrent) HF hospitalizations and CV death, ENTRESTO did not achieve statistical significance vs valsartan (RR 0.87; 95% CI: 0.75–1.01; *P*=.06).[6]

PARAGON-HF composite end point: ENTRESTO reduced the rate of the prespecified exploratory composite end point (total worsening HF events [HF hospitalizations and urgent HF visits] and CV death) by 14% (RR 0.86; 95% CI: 0.75–0.99) compared to valsartan, which was driven by a reduction in the rate of total worsening HF events.[13]

PARAGON-HF NT-proBNP: In a prespecified exploratory analysis, ENTRESTO decreased NT-proBNP from baseline by 24% at Week 16 and 19% by Week 48 compared to decreases of 6% and 3% on valsartan, respectively. NT-proBNP was analyzed in a subgroup and may not represent the full population. ENTRESTO CV and renal effects are due to increased peptides and decreased angiotensin II effects, which result in decreased NT-proBNP.[6]

*PROVE-HF was a single-arm, open-label study.
†PARAGON-HF defined HFpEF as patients with LVEF ≥45% and structural heart disease (LAE or LVH). PARAGLIDE-HF defined HFmrEF and HFpEF as patients with LVEF >40%. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.
‡Worsening HF event was defined as an HF hospitalization, emergency department visit, or out-of-hospital urgent HF visit, all requiring IV diuretics.
§In the 2022 HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II–III HFrEF (Class 1 recommendation). ENTRESTO was also included as a treatment option for HFmrEF (LVEF 41%–49%) and select patients with HFpEF (LVEF ≥50%), particularly for patients with LVEF on the lower end of the spectrum (Class 2b recommendation).
‖Event rate per 100 patient-years.

ACEi, angiotensin-converting enzyme inhibitor; ARR, absolute rate reduction; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; RR, rate ratio.

IMPORTANT SAFETY INFORMATION (cont)

Hypotension: ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension persists despite dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia), reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

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PARAGLIDE-HF: The first and only head-to-head study in stabilized HFmrEF and HFpEF* patients following a worsening HF event[12†]

PARAGLIDE-HF INCLUDED A DIVERSE RANGE OF US AND CANADIAN PATIENTS WHO WERE REFLECTIVE OF THOSE SEEN IN REAL-WORLD PRACTICE[12,14,15]

Study design: PARAGLIDE-HF was a multicenter, double-blind, randomized, controlled trial designed to assess changes in NT-proBNP, safety, and tolerability of ENTRESTO® (n=233) vs an active comparator, valsartan (n=233), in stabilized patients with HFmrEF and HFpEF (LVEF >40%) and elevated levels of natriuretic peptides who experienced a recent worsening HF event. Patients were randomized 1:1 to ENTRESTO (target dose: 97/103 mg BID) or valsartan (target dose: 160 mg BID), as tolerated. Patients were randomized to study drug following stabilization at the time of the worsening HF event, or within 30 days of a worsening HF event. Medically stable was defined by a systolic blood pressure >100 mmHg for the preceding 6 hours, no increase in IV diuretics or use of IV vasodilators within the last 6 hours, and no IV inotropes administered for 24 hours prior to randomization. All deaths, hospitalizations, and urgent HF events were adjudicated by an independent blinded committee.[12,16]

SELECT PATIENT DEMOGRAPHICS[12]

	ENTRESTO (n=233)	Valsartan (n=233)
Age, years	71.0 (61.0–78.0)	72.0 (62.0–79.0)
White race, n (%)	176 (75.5)	176 (75.5)
LVEF 41% to 60%, n (%)	178 (76.4)	179 (76.8)
Median LVEF, %	55.0	55.0
Medical history, n (%)		
• Hypertension	228 (97.9)	219 (94.0)
• Diabetes mellitus	107 (45.9)	119 (51.1)
• History of atrial fibrillation/atrial flutter	140 (60.1)	133 (57.1)
–Ongoing atrial fibrillation/atrial flutter	120 (51.5)	120 (51.5)
Examination and laboratory values		
• BMI (kg/m^2)	33.3 (27.3–41.3)	32.7 (27.0–39.5)
• eGFR (mL/min/1.73 m^2)	47.4 (36.4–62.2)	51.1 (39.4–64.8)
Prior medications, n (%)		
• ACEi/ARB	177 (76.0)	182 (78.1)
• MRA	75 (32.2)	60 (25.8)
• Beta blocker	185 (79.4)	169 (72.5)
• Loop diuretic	232 (99.6)	233 (100.0)
RASi-naive (not on an ACEi/ARB), n (%)	56 (24.0)	51 (21.9)

In the total patient population,[12,16]

- **52%** were female
- **30%** were of non-White race/ethnicity (22% were Black)
- **69.5%** were randomized in-hospital following stabilization (30.5% out of hospital)
- **33%** had no prior history of HF

*PARAGLIDE-HF defined HFmrEF and HFpEF as patients with LVEF >40%. The median LVEF was 55%. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.
†Worsening HF event was defined as an HF hospitalization, emergency department visit, or out-of-hospital urgent HF visit, all requiring IV diuretics.

eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor.

IMPORTANT SAFETY INFORMATION (cont)

Impaired Renal Function: Decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function.

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IN THE TOTAL POPULATION,

PARAGLIDE-HF: ENTRESTO® was superior to valsartan in reduction of NT-proBNP[12,17,18]

TOTAL POPULATION

ENTRESTO DEMONSTRATED A SIGNIFICANT REDUCTION IN NT-proBNP VS AN ARB AT WEEKS 4 AND 8[12]

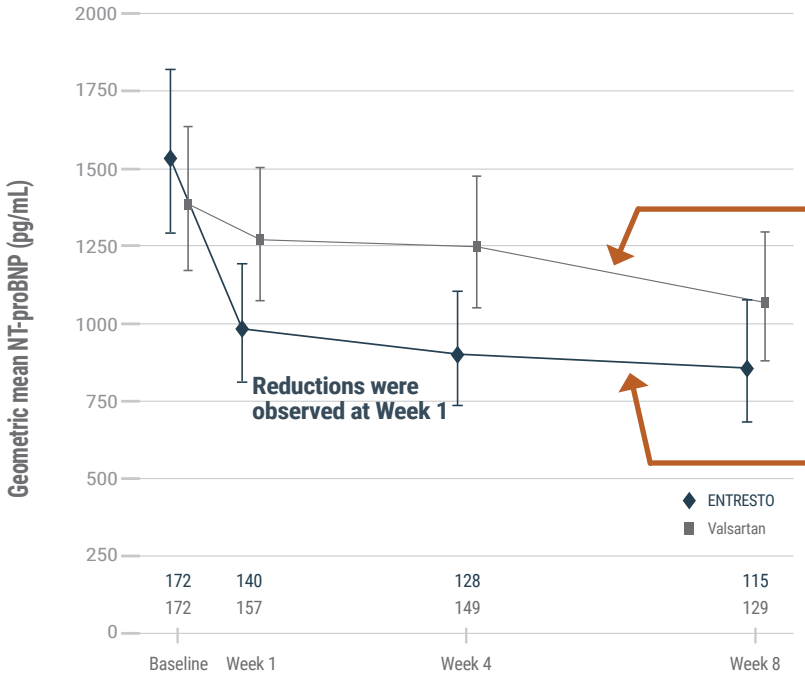
PRIMARY END POINT WAS MET: Time-averaged proportional change in NT-proBNP over time from baseline to Weeks 4 and 8

- ENTRESTO reduced NT-proBNP by **28%** (n=180) compared to **16%** with valsartan (n=197), with a proportional difference of **15%** (Ratio of change: 0.85; 95% CI: 0.73–0.999; *P*=.049)

PRESPECIFIED SUBGROUP ANALYSIS: LVEF ≤60%

In PARAGLIDE-HF, the prespecified subgroup analysis was not powered for determining the significance of the findings.

PATIENTS ON ENTRESTO HAD A GREATER REDUCTION IN NT-proBNP VS THOSE ON VALSARTAN[12,17,18]



A **rapid and sustained** reduction in NT-proBNP was observed at Weeks 4 and 8 with ENTRESTO.[12]

14% **REDUCTION WITH VALSARTAN**
from baseline to Weeks 4 and 8
(Ratio of change: 0.8582; 95% CI: 0.7570–0.9729)
n=151

33% **REDUCTION WITH ENTRESTO**
from baseline to Weeks 4 and 8
(Ratio of change: 0.6652; 95% CI: 0.5828–0.7593)
n=136

22% proportional change in NT-proBNP from baseline to Weeks 4 and 8 vs valsartan
(Ratio of change: 0.78, 95% CI: 0.65–0.93)

A decrease in NT-proBNP of >30% from baseline has been associated with a reduced risk of CV death and HF hospitalization[4]

Study limitations: The sample size was relatively modest. In addition, approximately 19% of patients did not contribute to the primary end point given the lack of NT-proBNP data. Limitations of this analysis are compounded by the inherent limitations when examining subgroups, including reduced sample size, selection bias, multiple comparisons, and lack of power.[12]

IMPORTANT SAFETY INFORMATION (cont)

Impaired Renal Function (cont): ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

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PARAGLIDE-HF: Secondary efficacy end points showed numerical differences favoring patients on ENTRESTO®[12]

In PARAGLIDE-HF, secondary end points were not powered for determining the significance of the findings.

WIN RATIO (TOTAL POPULATION)

The win ratio numerically favored patients on ENTRESTO vs those on valsartan[12]

19% ▲ **NUMERICALLY FAVORED ENTRESTO**

vs valsartan (NS)
Win ratio: 1.19 (95% CI: 0.93–1.52)

Win-ratio analysis (composite hierarchical outcome) consisted of:

Priority ↓
- Time to CV death
- Number and timing of HF hospitalizations
- Number and timing of urgent HF visits*
- Time-averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8

Across all components, each pairwise comparison resulted in the following:
- 36.9% of wins were with patients on ENTRESTO
- 31% of wins were with patients on valsartan
- 32.1% of comparisons ended in ties

WIN RATIO (PRESPECIFIED SUBGROUP ANALYSIS: LVEF ≤60%)

In patients with LVEF ≤60%, the win ratio numerically favored patients on ENTRESTO vs those on valsartan[12]

46% ▲ **NUMERICALLY FAVORED ENTRESTO**

vs valsartan
Win ratio: 1.46 (95% CI: 1.09–1.95)

Across all components, each pairwise comparison resulted in the following:
- 37.9% of wins were with patients on ENTRESTO
- 26% of wins were with patients on valsartan
- 36.1% of comparisons ended in ties

Wins for individual components:
- Time to CV death: 3.3% with ENTRESTO vs 2.3% with valsartan
- Number and timing of HF hospitalizations: 12.9% with ENTRESTO vs 8.9% with valsartan
- Number and timing of urgent HF visits*: 2.4% with ENTRESTO vs 1.3% with valsartan
- Change in NT-proBNP: 29% with ENTRESTO vs 20.2% with valsartan

COMPOSITE CV OUTCOMES END POINT (TOTAL POPULATION)

A numerically reduced rate in a composite end point of total HF hospitalizations, urgent HF visits,* and CV death was seen in patients on ENTRESTO vs those on valsartan driven by reduction in HF hospitalizations.[12]

- **17% relative rate reduction in patients on ENTRESTO** vs valsartan (NS): RR 0.83 (95% CI: 0.57–1.23); 12.7% ARR†

Win-ratio methodology: The composite hierarchical outcome was analyzed by estimating the win ratio by pairwise comparison of every participant in the ENTRESTO group to every participant in the valsartan group sequentially at each level of the hierarchy to determine a winner. A tie occurred if during the pairwise comparison there were missing lab values for either patient, or the proportional difference in change in NT-proBNP was <25%. For comparisons, only those events that occurred in the time at risk that were common for both patients in the pair were used for analysis to define a win or tie. The estimated win ratio was calculated by taking the total number of wins in the ENTRESTO arm and dividing by the total number of wins in the valsartan arm. There are no multiplicity adjustments for win ratios.[12]

Study limitations: The sample size was relatively modest and the study was not powered for clinical events. This study was powered for changes in NT-proBNP. Secondary end points were not powered for determining the significance of the findings. Results should be interpreted with caution due to the short time frame and infrequency of events. Limitations of this analysis are compounded by the inherent limitations when examining subgroups, including reduced sample size, selection bias, multiple comparisons, and lack of power.[12]

*An urgent HF visit was defined as an adjudicated emergency department visit or an urgent clinic visit requiring IV diuretics and not requiring overnight hospitalization.[19]
†Exposure-adjusted rate per 100 patient-years.

NS, not significant.

IMPORTANT SAFETY INFORMATION (cont)

Hyperkalemia: Hyperkalemia may occur with ENTRESTO. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO may be required.

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium.

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PARAGLIDE-HF: Renal function results and adverse events of special interest

WORSENING RENAL FUNCTION SECONDARY EFFICACY OUTCOME END POINT[12]

In PARAGLIDE-HF, secondary end points were not powered for determining the significance of the findings.

38% ▼
RELATIVE RATE REDUCTION

vs valsartan (NS)
RR 0.62 (95% CI: 0.25–1.56)
34 events were observed with ENTRESTO® vs 46 with valsartan

Worsening renal function composite end point was defined as:

- Renal death
- Reaching end-stage renal disease
  or
- ≥50% decline in eGFR relative to baseline

SAFETY PROFILE

ADVERSE EVENTS OF SPECIAL INTEREST[12]

Adverse event, n (%)	**ENTRESTO (n=233)**	**Valsartan (n=233)**
Symptomatic hypotension	56 (24.0)	36 (15.5)
Hyperkalemia	45 (19.3)	43 (18.5)
Worsening renal function*	50 (21.5)	72 (30.9)
Angioedema	0	1

- No new safety signals were identified[12]
- The exposure-adjusted incidence rates of serious adverse events were 103 (122.2 per 100 patient treatment years) for the ENTRESTO group and 103 (122.2 per 100 patient treatment years) for the valsartan group
- There were 18 deaths in the ENTRESTO group (10 CV) and 26 deaths in the valsartan group (18 CV)

Study limitations: Safety data were collected for only 8 weeks; therefore, adverse events that take longer to transpire may not have appeared in this study. Safety information should be interpreted in the context of prior trials with a longer duration.[12]

*The worsening renal function adverse event of special interest was defined as an increase in serum creatinine of ≥0.5 mg/L and worsening of the eGFR (mL/min/1.73 m^2) by ≥25%.

IMPORTANT SAFETY INFORMATION (cont)

ARBs: Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

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Heart failure is a progressive disease. Don't wait[20]:

From **HFrEF to HFpEF** in patients with **LVEF ≤60%, make ENTRESTO®** **an ESSENTIAL** part of your appropriate patients' heart failure treatment today

2022 AHA/ACC/HFSA HF Guideline Recommended in HFrEF* + Included in the 2023 ACC ECDP for HFpEF†

In PARAGON-HF

Expanded Approval to Include HFpEF‡ With LVEF ≤60% (Median LVEF 57%)[6,7]

In PARAGLIDE-HF

Diverse and Inclusive Patient Population[12]

Superior to an ARB[12]
PARAGLIDE-HF adds to the body of evidence of ENTRESTO data by demonstrating superiority in reduction of NT-proBNP vs valsartan in patients with HFmrEF and HFpEF§ from baseline to Weeks 4 and 8

Multiple Secondary Efficacy End Points Studied[12||]

No New Safety Signals Observed[12]

PATIENT SUPPORT

Patient Support for Your Eligible Patients

For information on ENTRESTO support and resources

*NYHA Class II–III patients with HFrEF.
†The 2023 ACC ECDP for HFpEF advises the use of ARNi (ENTRESTO) in patients with HFpEF with LVEF <55% to 60% and advises an ARB should be considered when ARNi is not feasible due to contraindication, cost, or intolerance.
‡PARAGON-HF defined HFpEF as patients with LVEF ≥45% and structural heart disease (LAE or LVH). The median LVEF was 57%. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.
§PARAGLIDE-HF defined HFmrEF and HFpEF as patients with LVEF >40%. The median LVEF was 55%. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.
||In PARAGLIDE-HF, secondary end points were not powered for determining the significance of the findings.

References:
1. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393 **2.** Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol.* 2017;70(20):2476-2486. doi:10.1016/j.jacc.2017.08.074 **3.** Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of sacubitril/valsartan on N-terminal pro-b-type natriuretic peptide in heart failure with preserved ejection fraction. *JACC Heart Fail.* 2020;8(5):372-381. doi:10.1016/j.jchf.2020.03.002 **4.** Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* 2004;110(15):2168-2174. doi:10.1161/01.CIR.0000144310.04433.BE **5.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines [published correction appears in *J Am Coll Cardiol.* 2023;81(15):1551]. *J Am Coll Cardiol.* 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012 **6.** ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **7.** Vaduganathan M, Claggett BL, Greene SJ, et al. Potential implications of expanded US Food and Drug Administration labeling for sacubitril/valsartan in the US. *JAMA Cardiol.* 2021;6(12):1415-1423. doi:10.1001/jamacardio.2021.3651 **8.** McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11): 993-1004. doi:10.1056/NEJMoa1409077 **9.** Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure [published correction appears in *N Engl J Med.* 2019;380(11):1090]. *N Engl J Med.* 2019;380(6):539-548. doi:10.1056/NEJMoa1812851 **10.** Januzzi JL Jr, Prescott MF, Butler J, et al. Association of change in N-terminal pro-b-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA.* 2019;322(11):1085-1095. doi:10.1001/jama.2019.12821 **11.** Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655 **12.** Mentz RJ, Ward JH, Hernandez AF, et al. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. *J Am Coll Cardiol.* 2023;S0735-1097(23):05429-3. doi:10.1016/j.jacc.2023.04.019 **13.** US Food and Drug Administration. Novartis cardiovascular and renal drugs advisory committee briefing document, December 15, 2020. ENTRESTO® (sacubitril/valsartan) for chronic heart failure and preserved ejection fraction. Accessed May 3, 2023. https://www.fda.gov/media/144379/download **14.** Powell-Wiley TM, Ngwa J, Kebede S, et al. Impact of body mass index on heart failure by race/ethnicity from the Get With The Guidelines-Heart Failure (GWTG-HF) registry. *JACC Heart Fail.* 2018;6(3):233-242. doi:10.1016/j.jchf.2017.11.011 **15.** Kumar V, Redfield MM, Glasgow A, et al. Incident heart failure with mildly reduced ejection fraction: frequency, characteristics, and outcomes. *J Card Fail.* 2023;29(2):124-134. doi:10.1016/j.cardfail.2022.10.424 **16.** Mentz RJ, Ward JH, Hernandez AF, et al. Rationale, design and baseline characteristics of the PARAGLIDE-HF trial: sacubitril/valsartan vs valsartan in HFmrEF and HFpEF with a worsening heart failure event [published online ahead of print, February 14, 2023]. *J Card Fail.* 2023;S1071-9164(23)00040-4. doi:10.1016/j.cardfail.2023.02.001 **17.** Data on file. Study CLCZ696DUS01. Novartis Pharmaceuticals Corp; 2023. **18.** Mentz RJ, Ward JH, Hernandez AF, et al. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. *J Am Coll Cardiol.* 2023;S0735-1097(suppl):05429-3. doi:10.1016/j.jacc.2023.04.019 **19.** Data on file. Study CLCZ696DUS01. Novartis Pharmaceuticals Corp; 2021. **20.** Sabbah HN. Silent disease progression in clinically stable heart failure. *Euro J Heart Fail*. 2017;19:469-478. doi:10.1002/ejhf.7054

Start Early. Start Now. Start ENTRESTO.

IMPORTANT SAFETY INFORMATION (cont)

Common Adverse Events: In a clinical trial of patients with heart failure with reduced ejection fraction, the most commonly observed adverse events with ENTRESTO vs enalapril, occurring at a frequency of at least 5% in either group, were hypotension (18%, 12%), hyperkalemia (12%, 14%), cough (9%, 13%), dizziness (6%, 5%), and renal failure/acute renal failure (5%, 5%). No new adverse reactions were identified in a trial of the remaining indicated population.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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