Entresto®
(sacubitril/valsartan) tablets
24/26mg · 49/51mg · 97/103mg

Clinical Trials Summary

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**

Please see additional Important Safety Information throughout and on page 7, and click here for full Prescribing Information, including **Boxed WARNING**.

NOVARTIS

Aim

To determine whether ENTRESTO was superior to an ACEi (enalapril) at reducing the risk of the combined end point of CV death or HF hospitalization in patients with HFrEF

Study Design

SINGLE-BLIND RUN-IN PERIOD*
(6–8 weeks)

Median Exposure:
15 days; N=10,513

Enalapril
10 mg BID

36-hour washout†

Median Exposure:
29 days; N=9419

ENTRESTO
49/51 mg BID

ENTRESTO
97/103 mg BID

36-hour washout†

*All patients were on an ACEi or ARB prior to the run-in period.
†There were two 36-hour washout periods during the run-in period to minimize the potential risk of angioedema due to overlapping ACE–neprilysin inhibition: the first after completing the enalapril run-in period and the second after completing the ENTRESTO run-in period.

DOUBLE-BLIND PERIOD
(duration was event driven; median follow-up was 27 months; patients were treated for up to 4.3 years)

1:1 RANDOMIZATION

ENTRESTO
97/103 mg BID; n=4209

Enalapril
10 mg BID; n=4233

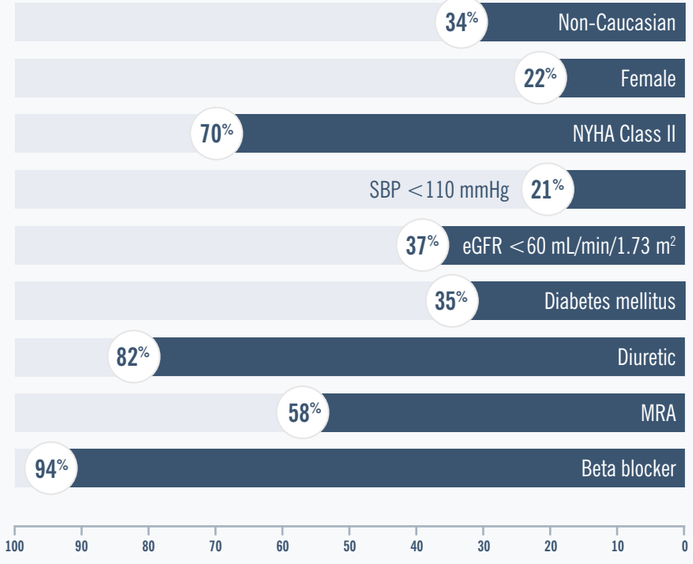
Patient Population

Overview
- 4209 patients on ENTRESTO (ARNi)
- 4233 patients on enalapril (ACEi)
- 27-month median follow-up
- Up to 4.3 years of treatment

Key Inclusion Criteria
- Symptomatic HF (NYHA Class II–IV)
- Systolic dysfunction
- LVEF ≤40%

Select Baseline Patient Characteristics (Full Population)

Mean LVEF: 29% **Mean age: 64 years**



Results

Primary End Point:
ENTRESTO reduced the risk of CV death or HF hospitalization as a first event vs enalapril.

20% RRR (HR 0.80; 95% CI: 0.73–0.87; ***P*<.0001**)

CV death: 20% RRR (HR 0.80; 95% CI: 0.71–0.89)[‡§]
HF hospitalization: 21% RRR (HR 0.79; 95% CI: 0.71–0.89)[‡]

Prespecified Exploratory End Point:
ENTRESTO reduced NT-proBNP by 32% from baseline (screening) to 4 weeks after randomization compared to 7% with enalapril.

The CV effects of ENTRESTO are attributed to increased levels of peptides and decreased angiotensin II effects, which resulted in decreased NT-proBNP.

Safety:
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%).

ENTRESTO and enalapril had comparable safety profiles.

Key Secondary End Points:
ENTRESTO reduced risk of death from any cause vs enalapril, driven entirely by the reduction in CV death.

16% RRR (HR 0.84; 95% CI: 0.76–0.93); ***P*<.001**

ENTRESTO had less decline in mean change in KCCQ-23 CS (–2.99; n=3643) vs enalapril (–4.63; n=3638) from baseline to 8 months. Clinically meaningful difference established as 5 points.

PARADIGM-HF utilized the KCCQ-23, a measurement of HRQoL assessing these domains: physical limitation, symptom frequency, symptom burden, symptom stability, self-efficacy, social limitation, and quality of life. Each domain is scored on a scale of 0-100; higher scores indicate better health status.

The KCCQ-23 CS represents the average of the symptom (frequency and burden) and physical limitation domains.

Analysis included all patients with at least 1 KCCQ data up to month 8. For patients who died, the worst score (0) was imputed for the CS at all subsequent scheduled visits.

Summary

- ENTRESTO was superior to an ACEi (enalapril) in reducing the risk of the composite end point of CV death or HF hospitalization, based on a time-to-event analysis among patients with HF and LVEF ≤40%
- The treatment effect reflected a reduction in both CV death and HF hospitalization
- The trial was stopped early due to overwhelming evidence of benefit
- In the largest HF clinical trial to date, ENTRESTO and enalapril had comparable safety profiles

Limitations

PARADIGM-HF NT-proBNP analysis limitation: NT-proBNP was drawn and analyzed in a subgroup of the total PARADIGM-HF patient population and therefore might not represent the entire cohort of patients studied.

PARADIGM-HF KCCQ-23 analysis limitations: Baseline KCCQ-23 CS in the overall PARADIGM-HF population was assessed at randomization. This may have resulted in higher baseline scores due to treatment during the run-in phase. Limited data exist assessing clinical meaningfulness of change scores in patients with relatively good baseline perceptions of HRQoL. The difference between ENTRESTO and enalapril treatment arms may have been driven in part by the treatment effect on HF hospitalizations.[4]

KCCQ-23 tool limitations: Two-week recall period. Missing scores in physical limitation domain may be missing because activities were not performed due to conditions other than HF.[5,6]

[‡]Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.
[§]Includes patients who had HF hospitalization prior to death.

IMPORTANT SAFETY INFORMATION (cont)

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.

IMPORTANT SAFETY INFORMATION (cont)

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.

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Aim

To determine whether ENTRESTO reduced the rate of the composite end point of total (first and recurrent) HF hospitalizations and CV death in patients with HFpEF

Study Design

SINGLE-BLIND RUN-IN PERIOD*
(6–8 weeks)

Valsartan* 40/80 mg BID → **ENTRESTO†** 49/51 mg BID

*Eligible patients were exposed to valsartan 80 mg BID for 1 to 2 weeks. Patients on low prestudy ACEi/ARB or those with tolerability concerns were first started on valsartan 40 mg BID for 1 to 2 weeks and then up-titrated to valsartan 80 mg BID for 1 to 2 weeks.
†Patients tolerating valsartan 80 mg BID for 1 to 2 weeks were switched to ENTRESTO 49/51 mg BID for 2 to 4 weeks.

DOUBLE-BLIND PERIOD
(median follow-up was 35 months; patients were treated for up to 4.7 years)

ENTRESTO 97/103 mg BID; n=2419

1:1 RANDOMIZATION

Valsartan 160 mg BID; n=2403

Patients were evaluated at study visits every 4 to 16 weeks during the first 48 weeks and every 12 weeks thereafter.

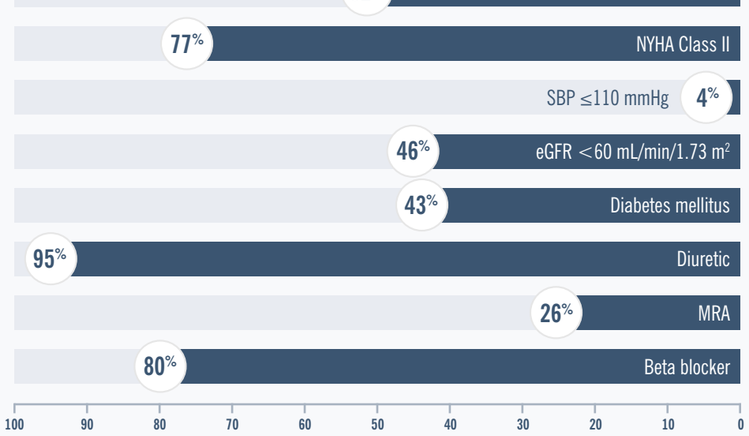
Patient Population

Overview
- 2419 patients on ENTRESTO (ARNi)
- 2403 patients on valsartan (ARB)
- 35-month median follow-up
- Up to 4.7 years of treatment

Key Inclusion Criteria
- Symptomatic HF with LVEF ≥45%
- Structural heart disease (LAE or LVH)
- No prior echocardiographic LVEF <40%

Select Baseline Patient Characteristics (Full Population)

Median LVEF: 57% | **Mean age: 73 years**



Results

Primary End Point:
For the primary composite end point 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**)

Safety:
No new adverse reactions were identified.

Prespecified Subgroup Analysis:
In patients with LVEF at or below the median of 57%, ENTRESTO reduced total HF hospitalizations and CV death vs valsartan.

22% RRR (RR 0.78; 95% CI: 0.64–0.95); ARR 3.6‡

This was driven by reduction in total HF hospitalizations.

Prespecified Exploratory Analysis:
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.

ENTRESTO reduced NT-proBNP by 24% from baseline (Week 16) compared to 6% with valsartan and by 19% from baseline (Week 48) compared to 3% with valsartan.

ENTRESTO CV and renal effects are due to increased peptides and decreased angiotensin II effects, which result in decreased NT-proBNP.

Summary

- ENTRESTO did not achieve statistical significance vs an ARB (valsartan) for the primary end point of total (first and recurrent) HF hospitalizations and CV death among patients with HF and LVEF of 45% or higher
- In a prespecified subgroup analysis, ENTRESTO reduced total HF hospitalizations and CV death vs valsartan in patients with LVEF at or below the median (45%–57%). This result led to an expanded label for use in patients with chronic HF with an LVEF below normal
- No new safety signals were identified

Limitations

PARAGON-HF NT-proBNP analysis limitation: NT-proBNP was analyzed in a subgroup and may not represent the full population.

‡Event rate per 100 patient-years.

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.

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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PIONEER-HF[11]

Aim

To compare the efficacy and safety of initiation of ENTRESTO and enalapril, after hemodynamic stabilization among patients with HFrEF who were hospitalized for acute decompensated HF

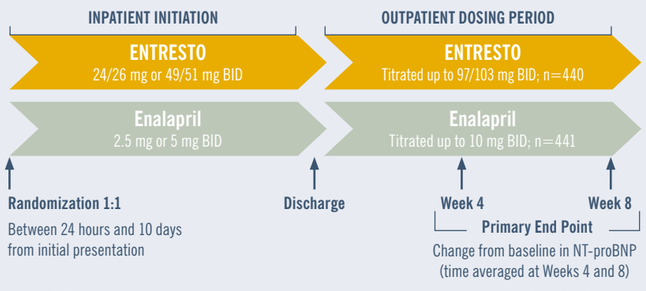
Study Design

Initial dose of study drug was determined by SBP at randomization

- **SBP 100 to <120 mmHg**
  - Dose level 1: ENTRESTO 24/26 mg BID or enalapril 2.5 mg BID
- **SBP ≥120 mmHg**
  - Dose level 2: ENTRESTO 49/51 mg BID or enalapril 5 mg BID

Patients taking low-dose or no ACEi/ARB at randomization were initiated on ENTRESTO 49/51 mg if their SBP was ≥120 mmHg. Patients were up-titrated as early as Week 1 and again at Weeks 2, 4, and 6 up to ENTRESTO 97/103 mg BID or enalapril 10 mg BID, as tolerated, based on their blood pressure.

Follow labeled dosing recommendations.



Patients (in-hospital) randomized to the enalapril treatment group received enalapril from the first dose. Patients (in-hospital) randomized to the ENTRESTO treatment group received 2 doses of placebo before receiving any dose of ENTRESTO to ensure the minimum 36-hour washout period prior to initiation.

Patient Population

Overview

- 440 patients on ENTRESTO (ARNi)
- 441 patients on enalapril (ACEi)

Key Inclusion Criteria

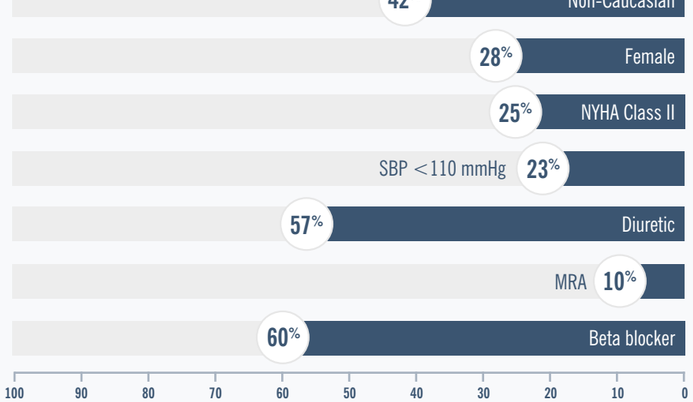
- Hemodynamically stabilized following hospitalization for acute decompensated HF:
  - SBP ≥100 mmHg and no symptomatic hypotension for the preceding 6 hours
  - No intensification of IV diuretics and no IV vasodilators (including IV nitrates) during the preceding 6 hours
  - No IV inotropes during the preceding 24 hours
- NYHA Class II–IV
- NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL
- LVEF ≤40%

Key Laboratory Measurements at Screening

- Median **NT-proBNP** 4812 pg/mL
- Median **BNP** 1063 pg/mL

Select Baseline Patient Characteristics (Full Population)

Median LVEF*: 24%–25% | **Mean age: 61 years**



*The median LVEF was 24% for the ENTRESTO group and 25% for the enalapril group.

Results

Primary End Point:

Time-averaged proportional change in NT-proBNP at 4 and 8 weeks: ENTRESTO 47%, enalapril 25%

Ratio of Change 0.71 (95% CI: 0.63–0.81; ***P*<.001**)

Key Safety End Points:

No significant differences were seen in rates of worsening renal function, hyperkalemia, symptomatic hypotension, or angioedema between ENTRESTO or enalapril.

Summary

- Initiation of ENTRESTO led to a 47% reduction in NT-proBNP concentration in stabilized HFrEF patients who had been admitted for acute decompensated HF. This reduction was significantly greater than that observed (25%) with an ACEi (enalapril)
- Previous studies have seen that a decrease in NT-proBNP >30% was associated with reduced risk of CV death and HF hospitalization[12,13]
- No significant differences were seen in key safety end points

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.

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 nonsteroidal 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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Aim

To assess the effect of ENTRESTO vs valsartan on changes in NT-proBNP, safety, and tolerability among stabilized patients with HFmrEF and HFpEF with a recent WHF event*

Study Design

Initial dose of study drug was determined by patient's previous dose or exposure to ACEi/ARB prior to a WHF event* or randomization

- **Patients not taking an ACEi/ARB, taking a low dose of an ACEi/ARB, or eGFR of ≥20 and <30 mL/min/1.73 m²**
  - Dose level 1: ENTRESTO 24/26 mg BID or valsartan 40 mg BID
- **Patients taking a high dose of an ACEi/ARB**
  - Dose level 2: ENTRESTO 49/51 mg BID or valsartan 80 mg BID

*WHF event was defined as an HF hospitalization, emergency department visit, or out-of-hospital urgent HF visit, all requiring IV diuretics.

DOUBLE-BLIND PERIOD

(median follow-up was 5.9 months)

Patients were randomized to study drug following stabilization at the time of the WHF event, or within 30 days of a WHF event.

ENTRESTO
Titrated up to 97/103 mg BID; n=233

1:1 RANDOMIZATION

Valsartan
Titrated up to 160 mg BID; n=233

Patients were evaluated at study visits at Day 7 (Week 1), followed by Day 28 (Week 4), Day 56 (Week 8), and then every ~112 days (16 weeks/4 months).

Patient Population

Overview

- 233 patients on ENTRESTO (ARNi)
- 233 patients on valsartan (ARB)
- 5.9-month median follow-up

Key Inclusion Criteria

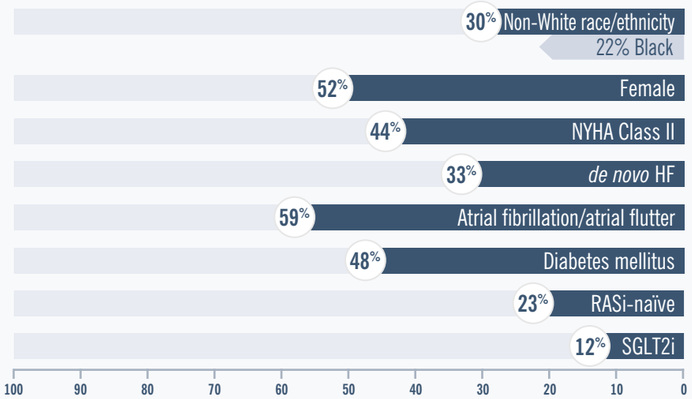
- Adult patients with HFmrEF (LVEF 41%–49%) or HFpEF (LVEF ≥50%)
  - With a recent WHF event* requiring IV diuretics
  - Who have been hemodynamically stabilized†
  - With elevated natriuretic peptides‡

Key Laboratory Measurements at Screening

- Median **NT-proBNP** 2009 pg/mL
- Median **BNP** 517 pg/mL

Select Baseline Patient Characteristics (Full Population)

- **Mean LVEF: 55%**
- **Mean BMI: 33 kg/m²**
- **LVEF ≤60%: 77%**
  41% to 49%: 23%
  50% to 60%: 54%
- **Mean age: 70 years**



†Medically stable was defined by a SBP >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.
‡NT-proBNP ≥500 pg/mL or BNP >150 pg/mL for patients in normal sinus rhythm; NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL for patients in atrial fibrillation.

All deaths, hospitalizations, and urgent HF events were adjudicated.

Results

Primary End Point:

Time-averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8: ENTRESTO 28% (n=180), valsartan 16% (n=197).

Ratio of Change 0.85 (95% CI: 0.73–0.999); ***P*=.049**

Prespecified Subgroup Analysis:

Not powered for determining the significance of findings

In patients with LVEF ≤60%:
Time-averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8: ENTRESTO 33% (n=136), valsartan 14% (n=151).

Ratio of Change 0.78 (95% CI: 0.65–0.93)

Safety:

No new safety signals were identified.

The adverse events of special interest with ENTRESTO vs valsartan were symptomatic hypotension (24.0%, 15.5%), hyperkalemia (19.3%, 18.5%), worsening renal function§ (21.5%, 30.9%), and angioedema (0 events, 1 event).

Secondary End Points:

Not powered for determining the significance of findings

The win-ratio analysis (composite hierarchical outcome of time to CV death, number and timing of HF hospitalizations, number and timing of urgent HF visits,‖ and time-averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8) numerically favored patients on ENTRESTO vs valsartan.

- Total population: win ratio 1.19 (95% CI: 0.93–1.52) (NS)
  - 36.9% of wins were with patients on ENTRESTO, 31% of wins were with patients on valsartan, and 32.1% of comparisons ended in ties
- In patients with LVEF ≤60%: win ratio 1.46 (95% CI: 1.09–1.95)
  - 37.9% of wins were with patients on ENTRESTO, 26% of wins were with patients on valsartan, and 36.1% of comparisons ended in ties

A numerically reduced rate in a composite end point of rate of CV death, total HF hospitalizations, and total urgent HF visits‖ was observed for patients on ENTRESTO vs valsartan driven by reduction in HF hospitalizations.

Total population: RR 0.83 (95% CI: 0.57–1.23); 12.7% ARR¶ (NS)

A numerically reduced rate in a worsening renal composite end point# was observed for patients on ENTRESTO vs valsartan.

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

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.*

Summary

- Initiation of ENTRESTO led to a 28% reduction in NT-proBNP concentration from baseline to Weeks 4 and 8 in stabilized HFmrEF/HFpEF patients who had a WHF event.* This reduction was superior to that observed with an ARB (valsartan, 16%)
  - In a prespecified subgroup analysis of patients with an LVEF ≤60%, ENTRESTO had a greater reduction in NT-proBNP concentration (33%) than that observed with an ARB (valsartan; 14%)
  - Previous studies have reported that a decrease in NT-proBNP >30% was associated with reduced risk of CV death and HF hospitalization.[12,13] 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)[19]
- Worsening renal function occurred more often in patients treated with valsartan and symptomatic hypotension occurred more often in patients treated with ENTRESTO. No new safety signals identified

Limitations

Primary end point 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.

Secondary end point 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 significance of 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.

Safety 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 longer duration.

§Increase in serum creatinine of ≥0.5 mg/dL and worsening of the eGFR (mL/min/1.73 m²) by ≥25%.
‖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.[20]
¶Exposure-adjusted rate per 100 patient-years.
#Renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline.

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.

IMPORTANT SAFETY INFORMATION (cont)

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

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Aim

To examine the correlation between changes in NT-proBNP and changes in cardiac structure and function in patients with HFrEF treated with ENTRESTO

Study Design

OPEN-LABEL TREATMENT PERIOD

ENTRESTO
97/103 mg BID*; N=794

Week 52

At each study visit (baseline, month 6, and month 12), a blood sample was sent to a central laboratory for measurement of plasma NT-proBNP. Following completion, echocardiograms were transmitted in a secure fashion to a core laboratory, where they were interpreted following completion of all study protocols in a temporally and clinically blinded fashion.

*ENTRESTO was initiated and titrated per the PI. Standard HF therapy was continued throughout the study with the exception of ACEi/ARB.

Patient Population

Overview

- Exploratory analysis
- 794 patients on ENTRESTO (outpatients)

Key Inclusion Criteria

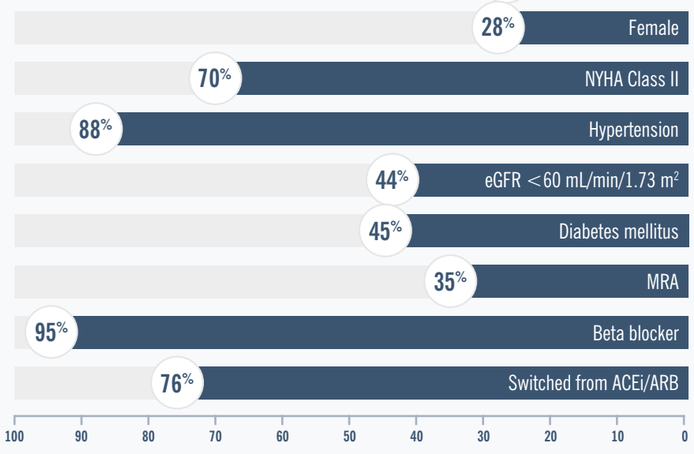
- NYHA Class II–IV
- LVEF ≤40% within the preceding 6 months and no subsequent documentation of EF >40%
- Stable dose of loop diuretic for the 2 weeks preceding study start

Key Laboratory and Remodeling Measurements at Baseline

- Median **NT-proBNP** 816 pg/mL
- Median **LVESVI** 61.68 mL/m^2
- Median **LVEDVI** 86.93 mL/m^2
- Median **LAVI** 37.76 mL/m^2
- Median **E/e'** 11.7

Select Baseline Patient Characteristics (Full Population)

Median LVEF: 28% **Mean age: 65 years**



†Race was investigator-determined, with potential risk for inaccuracy.

Results

Primary End Point:

Correlation (Pearson *r*) between change in echocardiographic remodeling parameters and NT-proBNP at 12 months, ***P*<.001**

Functional Measures:
– LVEF: *r*=-0.381
– E/e': *r*=0.269

Structural Measures:
– LVESVI: *r*=0.405
– LVEDVI: *r*=0.320
– LAVI: *r*=0.263

Secondary End Point:

Lower, yet significant, correlations were seen from baseline to 6 months, ***P*<.001.**

Remodeling measure	LVEF (%)	LVESVI (mL/m²)	LVEDVI (mL/m²)	LAVI (mL/m²)	E/e'
LS mean change 6 months	5.2‡	–8.7	–6.7	–4.4	–1.2
LS mean change 12 months	9.4‡	–15.3	–12.3	–7.6	–1.3

Reduction in NT-proBNP was demonstrated at 6 months (35%) and 12 months (37%).§

Summary

Reduction in NT-proBNP concentration was significantly correlated with improvements in markers of cardiac volume and function, including LVEF, among patients with HFrEF who were treated with ENTRESTO for 12 months.

Limitations

PROVE-HF study limitations: Observational, single-group, open-label design. A broad range of factors may affect NT-proBNP concentrations besides cardiac remodeling. Multiple comparisons may have increased risk of type 1 error. Not all echocardiographic measurements were available at each time point.

‡Changes in LVEF are LS mean change values from baseline.
§LS geometric mean concentration changes from baseline NT-proBNP to follow-up.

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.

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.

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.

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.

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.

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.

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.

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 click here for full Prescribing Information, including **Boxed WARNING**.

Please see additional Important Safety Information throughout and on this page, and click here for full Prescribing Information, including **Boxed WARNING**.

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ABBREVIATIONS

ACEi=angiotensin-converting enzyme inhibitor
ARB=angiotensin II receptor blocker
ARNi=angiotensin receptor-neprilysin inhibitor
ARR=absolute rate reduction (PARAGON-HF)
BID=twice daily
BMI=body mass index
BNP=brain natriuretic peptide
CI=confidence interval
CS=Clinical Summary Score
CV=cardiovascular
E/e'=filling pressure (early diastolic filling velocity/early diastolic mitral annular velocity)
EF=ejection fraction
ESRD=end-stage renal disease
eGFR=estimated glomerular filtration rate
HF=heart failure
HFmrEF=HF with mildly reduced ejection fraction
HFpEF=HF with preserved ejection fraction
HFrEF=HF with reduced ejection fraction
HR=hazard ratio
HRQoL=health-related quality of life
IV=intravenous
KCCQ-23=Kansas City Cardiomyopathy Questionnaire-23
LAE=left atrial enlargement
LAVI=left atrial volume index
LS=least squares
LVEDVI=left ventricular end-diastolic volume index
LVEF=left ventricular ejection fraction
LVESVI=left ventricular end-systolic volume index
LVH=left ventricular hypertrophy
MRA=mineralocorticoid receptor antagonist
NT-proBNP=N-terminal prohormone of brain natriuretic peptide
NYHA=New York Heart Association
OR=odds ratio
PI=Prescribing Information
RASi=renin-angiotensin system inhibitor
RR=rate ratio
RRR=relative rate reduction (PARAGON-HF/PARAGLIDE-HF)
RRR=relative risk reduction (PARADIGM-HF)
SGLT2i=sodium-glucose co-transporter-2 inhibitor
SBP=systolic blood pressure
WHF=worsening heart failure

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