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QUESTIONS & ANSWERS

IN MOST PATIENTS WITH HEART FAILURE, HELP HEART FAILURE MEET HEART SUCCESS WITH ENTRESTO®

Start ENTRESTO to help reduce the risk of CV death and HF hospitalization.

CV, cardiovascular; HF, heart failure.

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**

NOVARTIS

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

THANK YOU
FOR YOUR INTEREST IN ENTRESTO®

Just because ENTRESTO was approved over 8 years ago, with over 1.8 million patients treated since launch, that doesn't mean you don't still have questions.[1,2]

We are providing this booklet to answer questions that are frequently asked by health care professionals like you, pertaining to "WHY," "WHO," and "HOW" to prescribe ENTRESTO.

Additional info is available at **ENTRESTOHCP.com**.

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.

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WHO is an appropriate patient for ENTRESTO?

HOW do I manage treatment for patients on ENTRESTO?

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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ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARR, absolute risk reduction; BNP, brain natriuretic peptide; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; NNT, number needed to treat; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RAS, renin-angiotensin system.

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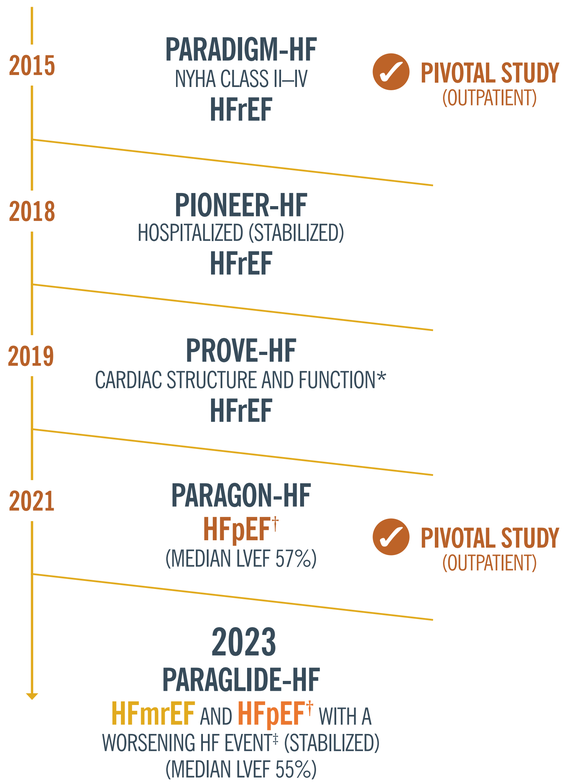
WHY should I consider ENTRESTO®?

Q1: Why should I consider ENTRESTO for patients with HF with LVEF ≤60%?

A: ENTRESTO is prescribed across the spectrum of patients **from HFrEF to HFpEF with LVEF ≤60%.**[1]

AS THE FIRST AND ONLY ARNi, ENTRESTO HAS PAVED THE WAY IN PATIENTS WITH LVEF ≤60% [1,3-8]



*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, ED visit, or out-of-hospital urgent HF visit, all requiring IV diuretics.

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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Q2: What does the 2022 AHA/ACC/HFSA HF Guideline tell us about using ENTRESTO?

A: The 2022 HF Guideline recognizes ENTRESTO in 3 HF patient populations.[9]

THE 2022 HF GUIDELINE EXPANDS ITS RECOGNITION OF ENTRESTO INTO MORE HF PATIENT TYPES[9]

- ENTRESTO is strongly recommended in **HFrEF**[§] to reduce **MORBIDITY AND MORTALITY.** In patients with chronic symptomatic **HFrEF**[§] who tolerate an ACEi/ARB, replacement by ENTRESTO is recommended to further reduce **MORBIDITY AND MORTALITY** (Class 1 recommendation)[9]
- Consider ENTRESTO in **HFmrEF** to reduce the risk of **HF HOSPITALIZATION AND CV MORTALITY** (Class 2b recommendation)
- Consider ENTRESTO in **HFpEF** to decrease **HF HOSPITALIZATIONS**, particularly for patients with LVEF on the lower end of the spectrum (Class 2b recommendation)[||]

  ~80% of patients with HF have LVEF ≤60% and may be appropriate for ENTRESTO[3]

- ENTRESTO is the only branded medication deemed by the 2022 HF Guideline to provide high economic value[9¶]
  - In patients with chronic symptomatic HFrEF, treatment with ENTRESTO instead of an ACEi provides high economic value

¶Value statements for select therapies were created based upon benchmarks adopted by AHA/ACC/HFSA where high-quality cost-effectiveness studies of the intervention had been published.

IN ADDITION, THE 2023 ACC EXPERT CONSENSUS DECISION PATHWAY (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.[10]

§NYHA Class II-III patients with HFrEF.
||In PARAGON-HF, HFpEF was defined as LVEF ≥45% with structural heart disease (LAE or LVH) and no prior echocardiographic LVEF <40%. Median LVEF was 57%. In a prespecified subgroup analysis of patients with LVEF at or below the median, ENTRESTO reduced the rate of total HF hospitalization and CV death vs valsartan, driven by reduction in HF hospitalization: RR 0.78 (95% CI: 0.64–0.95); 3.6 ARR#. HF hospitalization component: RR 0.75 (95% CI: 0.60–0.95); 3.6 ARR#. CV death component: HR 0.99 (95% CI: 0.77–1.26); 0.1 ARR#.[1,4,11]
#Event rate per 100 patient-years.

ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; ARR, absolute rate reduction; CI, confidence interval; ED, emergency department; HR, hazard ratio; IV, intravenous; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; RR, rate ratio.

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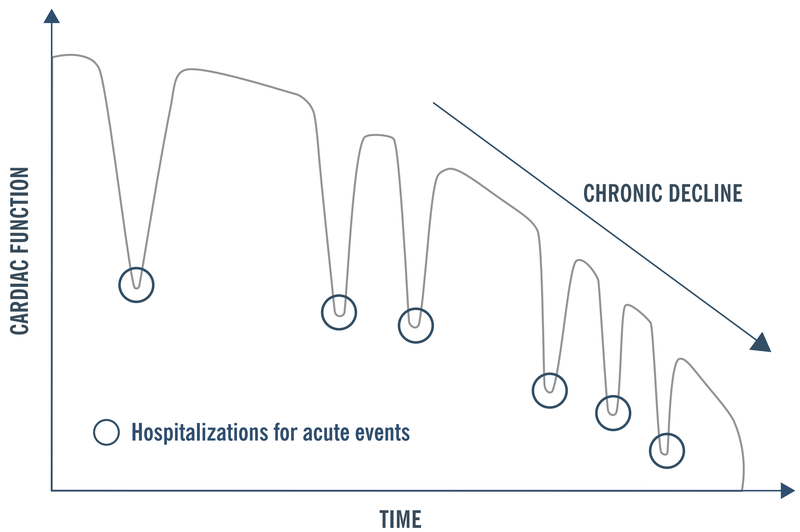
Q3: Why should I consider utilizing ENTRESTO®, even if a patient seems stable on their current treatment plan?

A: Heart failure is a continuous, progressive disease. Even if your patients seem clinically stable, their underlying disease may be progressing.[12-14]



Adapted from Mesquita ET, Jorge AJL, Rabelo LM, et al. *Int J Cardiovasc Sci*. 2017;30(1):81–90.
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In a study with a median follow-up of 27 months, 1 hospitalization put HFrEF patients at up to 6x greater risk of death vs those who had not been hospitalized for HFrEF.[1,15]*

*Post hoc analysis of the PARADIGM-HF study, a multinational, randomized, double-blind trial comparing sacubitril/valsartan to enalapril in 8442 symptomatic (NYHA Class II–IV) HFrEF patients (LVEF ≤40%). For the primary end point, composite of CV death or first HF hospitalization, sacubitril/valsartan was superior to enalapril ($P<.0001$). This post hoc analysis examined the association of first nonfatal events—either HF hospitalization, ED visit, or outpatient intensification of HF therapy—with subsequent mortality during the trial. For the 1107 patients in the study who had a hospitalization for worsening HF as a first event, vs those with no event, the HR for mortality was 6.1 (95% CI: 5.4–6.8).

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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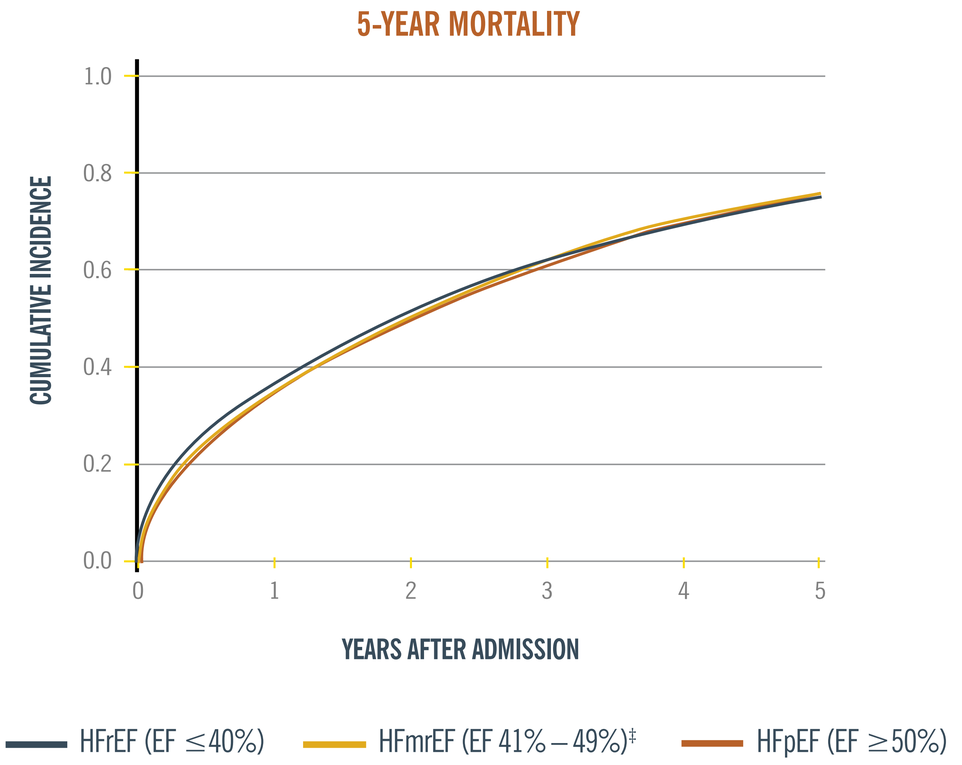
HFmrEF and HFpEF have a similar prognosis to HFrEF—**it is critical to treat these patients urgently.**[10,16]

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[16†]



†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 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.
GWTG-HF, Get With The Guidelines®-Heart Failure.

Q4: Can ENTRESTO® be initiated in the inpatient setting? By whom?

A: Hospitalists, cardiologists, PCPs, and APPs can all have a part in initiating treatment with ENTRESTO.[1,3-8]

The 2022 HF Guideline recommends in patients with HFrEF hospitalized for acute decompensated heart failure, GDMT should be initiated during hospitalization after clinical stability is achieved.[9]

According to the 2023 ACC ECDP for HFpEF, treatment of HFpEF has been historically limited to managing patients' comorbidities—which is why, now, the ECDP calls for **timely implementation** of GDMT in HFpEF management.[10]

Q5: What makes ENTRESTO different from other RAS inhibitors?

A: Overactivation of RAAS is an important factor contributing to the progression of HF.[17] RAS inhibition (RASi) is a recognized component of HF patient management.[9,10] ENTRESTO is designed specifically to treat HF. It's the only treatment in the HF landscape of its kind. ENTRESTO has a dual MOA that targets 2 complementary HF pathways through valsartan—an ARB that has been used for years to treat HF through RAS inhibition—and sacubitril—a neprilysin inhibitor that works unlike any other HF treatment and can only be found in ENTRESTO.[1,18,19]

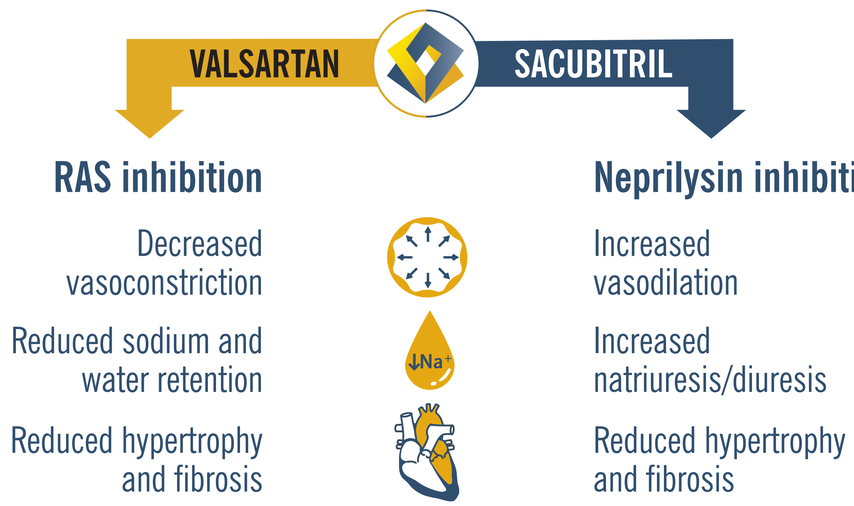
Please refer to the figure below Q7 for the ENTRESTO MOA.

Q6: What are the effects of neprilysin inhibition?

A: Neprilysin is an enzyme that breaks down certain vasoactive agents, such as natriuretic peptides, in the body. Neprilysin inhibition increases levels of these peptides. As you may know, some of these vasoactive peptides are associated with beneficial effects such as vasodilation, natriuresis, and aldosterone suppression.[1,18]

Q7: Why was sacubitril not studied on its own?

A: Neprilysin degrades vasoactive agents (such as natriuretic peptides) and vasoconstrictive agents (such as angiotensin II). Sacubitril inhibits neprilysin, increasing the levels of both of these agents. Therefore, it is necessary to block the effects of the increased levels of angiotensin II with an ARB. For this reason, ENTRESTO combines neprilysin inhibition, enhancing vasodilation, with an angiotensin receptor blockade to inhibit the effects of angiotensin II.[1,20]



Blocking 1 pathway with ACEi/ARB is not enough

APP, advanced practice provider; GDMT, guideline-directed medical therapy; MOA, mechanism of action; PCP, primary care physician; RAAS, renin-angiotensin-aldosterone system.

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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Q8: What was the efficacy of ENTRESTO® vs enalapril in the PARADIGM-HF trial, including the ARR and NNT, in patients with HFrEF?

A: In the PARADIGM-HF study, the primary end point was the time to first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.[1]

PROVEN RISK REDUCTION IN COMPOSITE END POINT, WITH CONSISTENT RESULTS ACROSS INDIVIDUAL CV DEATH AND HF HOSPITALIZATION COMPONENTS[1,5]

PRIMARY END POINT

20% RELATIVE RISK REDUCTION
IN CV DEATH OR HF HOSPITALIZATION AS A FIRST EVENT
4.7% ARR, *P*<.0001
NNT: 21
vs enalapril

20% RELATIVE RISK REDUCTION
IN CV DEATH*†
3.2% ARR,
NNT: 32
vs enalapril

21% RELATIVE RISK REDUCTION
IN FIRST HF HOSPITALIZATION*
2.8% ARR,
NNT: 36
vs enalapril

The ARR is the absolute difference in outcome between the ENTRESTO arm and the enalapril arm. The NNT is an estimation of the impact of a therapy using the number of patients that need to be treated in order to prevent 1 event. In other words, with an NNT of 21, for every 21 patients treated, 1 event was prevented over the duration of the study.[21]

PARADIGM-HF study design: PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in 8442 symptomatic (NYHA Class II–IV) adult HFrEF patients (LVEF ≤40%). After discontinuing their existing ACEi or ARB therapy, patients entered sequential single blind, run-in periods during which they received enalapril, followed by ENTRESTO. Patients who successfully completed the run-in periods were then randomized to receive either ENTRESTO 200 mg BID (n=4209) or enalapril 10 mg BID (n=4233). The median follow-up duration was 27 months, and patients were treated up to 4.3 years.[1]

*Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.
†Includes all CV deaths, with or without prior hospitalization.

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).

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Q9: What was the efficacy of ENTRESTO vs valsartan in the PARAGON-HF trial in patients with LVEF ≤60%?

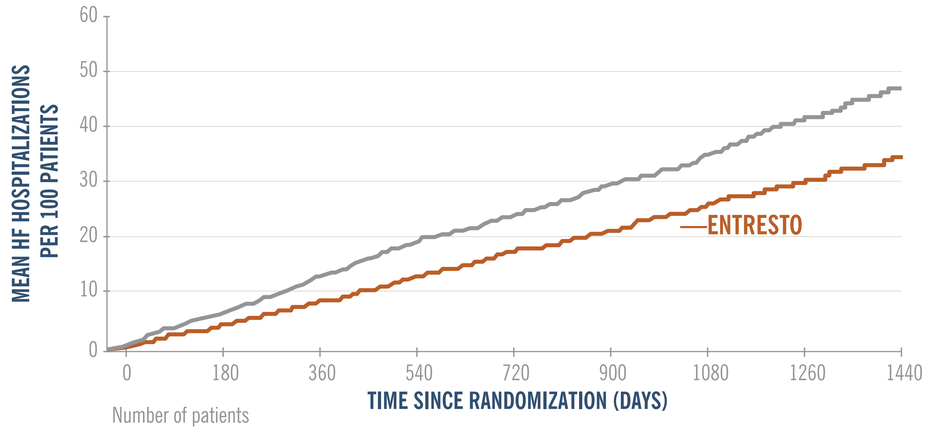
A: ENTRESTO REDUCED TOTAL HF HOSPITALIZATIONS AND CV DEATH[1,11]
In a prespecified subgroup analysis of PARAGON-HF patients with LVEF at or below the median (57%)‡:

22% RELATIVE RATE REDUCTION IN COMPOSITE END POINT VS VALSARTAN
Driven by reduction in HF hospitalizations
RR 0.78 (95% CI: 0.64–0.95); 3.6 ARR§
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)

ENTRESTO REDUCED TOTAL HF HOSPITALIZATIONS VS VALSARTAN[11]
Components of the composite in patients with LVEF at or below the median (57%)‡:

25% RELATIVE RATE REDUCTION IN TOTAL HF HOSPITALIZATIONS[11]
RR 0.75 (95% CI: 0.60–0.95); 3.6 ARR§
CV death: HR 0.99 (95% CI: 0.77–1.26); 0.1 ARR§

TOTAL HF HOSPITALIZATIONS IN PATIENTS WITH LVEF AT OR BELOW THE MEDIAN (57%)[1,11‡]



Number of patients								
ENTRESTO	1239	1219	1196	1156	1128	928	577	277	93
Valsartan	1256	1226	1199	1168	1141	938	566	292	100

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, structural heart disease [LAE or LVH], and no prior echocardiographic LVEF <40%). 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.[1,4]

‡LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.
§Event rate per 100 patient-years.

BID, twice daily.

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Q10: What effect does ENTRESTO® have on levels of BNP and NT-proBNP?

A: A decrease in **NT-proBNP of >30%** from baseline has been associated with a reduced risk of CV death and HF hospitalization.[22] The 2022 HF Guideline strongly recommends measuring BNP or NT-proBNP levels at admission in patients hospitalized for HF to establish prognosis (Class 1 recommendation).[9] ENTRESTO CV effects are due to increased peptides and decreased angiotensin II effects, which result in decreased NT-proBNP.[1]

In a prespecified exploratory end point of **PARADIGM-HF**, ENTRESTO resulted in a **32% reduction in NT-proBNP** vs 7% for enalapril at 4 weeks. NT-proBNP was analyzed in a subgroup and may not represent the full population.[1,23,24]

In **PIONEER-HF**, ENTRESTO resulted in a **47% reduction in NT-proBNP** from baseline vs 25% for enalapril at Weeks 4 and 8—a 29% greater reduction (Ratio of change: 0.71; 95% CI: 0.63–0.81; $P<.001$).[6]

In a prespecified exploratory analysis in **PARAGON-HF**, ENTRESTO decreased NT-proBNP by **24%** from baseline 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.[1]

In **PARAGLIDE-HF**, the primary end point was 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) from baseline to Weeks 4 and 8, with a proportional difference of **15%** (Ratio of change: 0.85; 95% CI: 0.73–0.999; $P=.049$).[8]

PIONEER-HF study design: PIONEER-HF was a multicenter, randomized, double-blind, active-controlled clinical trial of in-hospital initiation of ENTRESTO (n=440), compared with enalapril (n=441), among HFrEF patients (LVEF ≤40%) who had been stabilized following admission for ADHF.
PARAGLIDE-HF 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.[25]

*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, ED visit, or out-of-hospital urgent HF visit, all requiring IV diuretics.

ADHF, acute decompensated heart failure.

IMPORTANT SAFETY INFORMATION (cont)

Impaired Renal Function (cont): 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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Q11: What was the effect of ENTRESTO vs valsartan in the PARAGLIDE-HF trial in stabilized HFmrEF and HFpEF patients following a worsening HF event?

A: TOTAL POPULATION

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

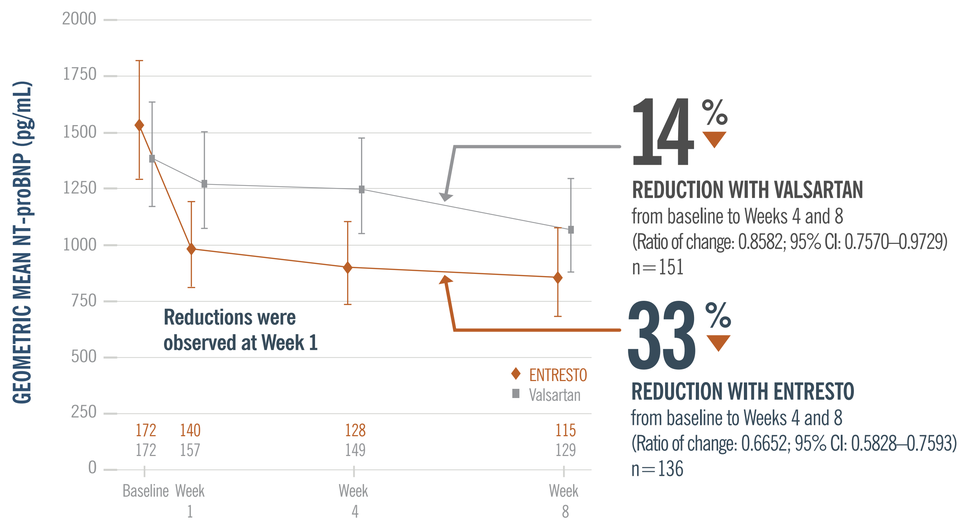
PRIMARY END POINT WAS MET: Time-averaged proportional change in NT-proBNP over time from baseline to Weeks 4 and 8

- 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[8,26,27]



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

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)

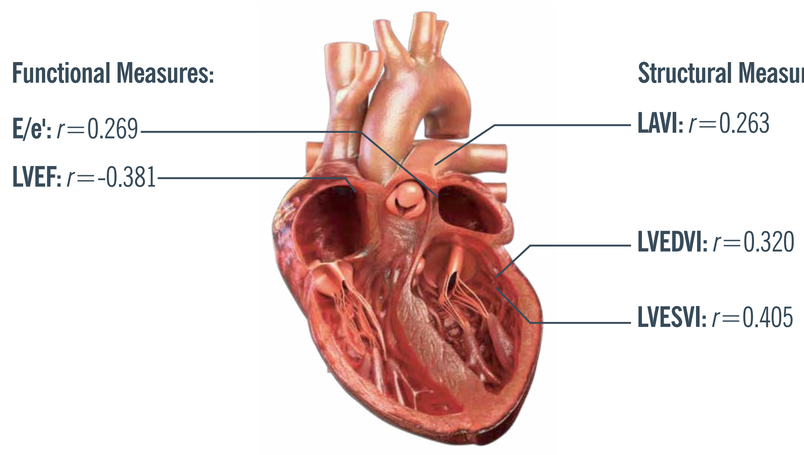
PARAGLIDE-HF study limitations: The sample size was relatively modest. In addition, approximately 19% of patients did not contribute to the primary end point given the lack of NT-proBNP data. Limitations of this analysis are compounded by the inherent limitations when examining subgroups, including reduced sample size, selection bias, multiple comparisons, and lack of power.[8]

Q12: What effect did ENTRESTO have on measures of biomarkers and measures of cardiac structure and function in HFrEF?

A: PROVE-HF—a 52-week, single-group, prospective, open-label Phase IV study of 794 adult HFrEF (LVEF ≤40%) outpatients initiated on ENTRESTO—assessed the correlation between changes in NT-proBNP and measures of cardiac structure and function.[7,28-32]

PROVE-HF PRIMARY END POINT

The primary end point was correlation (Pearson *r*)* between change in echocardiographic remodeling parameters and NT-proBNP at 12 months ($P<.001$).[7]



PROVE-HF study limitations[7]

- 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

*A Pearson correlation coefficient (Pearson *r*) measures how strong the association is between 2 variables. It ranges from 1 (exactly correlated) to -1 (exactly inversely correlated).

E/e', filling pressure (early diastolic filling velocity/early diastolic mitral annular velocity); LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

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.

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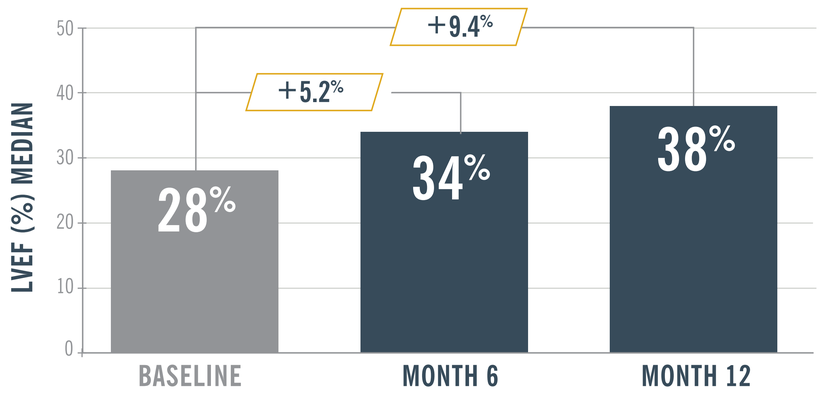
In PROVE-HF, reduction in NT-proBNP significantly correlated with reverse remodeling measures.[7]

ENTRESTO IMPROVED KEY ECHOCARDIOGRAPHIC MEASURES OF CARDIAC REMODELING, INCLUDING INCREASED LVEF, AND REDUCED NT-proBNP[7]

LS mean change† in LVEF over time:



Remodeling measure	LS mean change 6 months	LS mean change 12 months
LVESVI (mL/m²)	-8.7 ↓	-15.3 ↓
LVEDVI (mL/m²)	-6.7 ↓	-12.3 ↓
LAVI (mL/m²)	-4.4 ↓	-7.6 ↓
E/e'	-1.2 ↓	-1.3 ↓

Reduction in NT-proBNP was demonstrated at 6 months (35%) and 12 months (37%)[7‡]

The primary end point was the correlation between change in NT-proBNP and cardiac remodeling parameters at 12 months. A secondary end point was the correlation between change in NT-proBNP and change in cardiac remodeling parameters at 6 months.

Lower yet significant correlations were seen from baseline to 6 months.

†LVEF (%) are median values. Changes in LVEF are LS mean change values from baseline.
‡LS geometric mean concentration changes from baseline NT-proBNP to follow-up.

LS, least-square.

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Q13: What data does ENTRESTO® have in a real-world setting?

A: In addition to demonstrated outcomes from landmark clinical studies, ENTRESTO has gained experience in both real-world inpatient and outpatient settings.[1,33]

In a real-world analysis within the Cleveland Clinic Health System, ENTRESTO patients had lower HF hospitalization rates vs an ACEi/ARB over 6 months[33]:

DECREASE IN RATE OF HF HOSPITALIZATION[1,11,33]

54% **RELATIVE ODDS REDUCTION in HF hospitalization rate** vs an ACEi/ARB

OR 0.46 (95% CI: 0.31–0.67)

3.3% ENTRESTO (n/N=59/1794) vs 6.3% ACEi/ARB (n/N=112/1794)

THESE REAL-WORLD DATA COMPLEMENT CLINICAL TRIAL DATA FROM THE PARADIGM-HF AND PARAGON-HF CLINICAL TRIALS[1,5,11]

- In PARADIGM-HF, ENTRESTO reduced the risk of HF hospitalization* in patients with HFrEF by 21% (2.8% ARR) vs enalapril. Please see study design on page 13
- In PARAGON-HF, ENTRESTO reduced the rate of total HF hospitalization in patients with LVEF below normal by 25% (3.6 ARR†) vs valsartan. Please see study design on page 14

DISTRIBUTION OF BASELINE EF[33]

	ENTRESTO (n=1794)	**ACEi/ARB** (n=1794)
Mean (SD)	29 (9.9)	29 (9.7)
10% to 39%; n (%)	1535 (85.6)	1535 (85.6)
40% to 49%; n (%)	194 (10.8)	194 (10.8)
50% to 59%; n (%)	53 (3.0)	53 (3.0)
60% to 65%; n (%)	12 (0.67)	12 (0.67)

*Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.
†Event rate per 100 patient-years.
OR, odds ratio.

IMPORTANT SAFETY INFORMATION (cont)

Hyperkalemia (cont): 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.

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

Real-World Analysis Study Methods[33]

- Within a large multistate health care system (OH and FL) with 12 hospitals and over 100 outpatient practices, adult patients prescribed ENTRESTO were matched to patients prescribed an ACEi/ARB
- The study cohort was retrospectively identified from August 2015 through July 2018, which preceded the FDA approval of the adult chronic HF indication of ENTRESTO to include HF patients with LVEF below normal in February 2021. The patients identified from these claims data and included in this analysis are considered to reflect the current on-label patient population of ENTRESTO‡
- Matching variables: age, sex, and EF%; hospital care vs outpatient care at baseline; index (baseline) date; Charlson Comorbidity Index; systolic blood pressure
- HF hospitalizations were compared between the 2 groups
- Eligible patients must have had HF and available EF data in the electronic medical record in order to be included

Real-World Analysis Study Population[33]

- Of 1794 patients who initiated ENTRESTO, 95.1% initiated it in an outpatient department
- Baseline mean (SD) age was 64.2 (13.0) years; male: 70.3%
- Baseline EFs are shown in opposite table

Real-World Analysis Limitations[33]

- Patients with EF of 40% to 65% are underrepresented (<15%) in the sample identified
- Patients were treated in 1 health care system
- Medication decisions could have been influenced by system, provider, and patient factors
- Patients were not randomized to groups
- Nonstudied factors could have influenced findings as is inherent in such retrospective analyses

‡Prior to February 2021, ENTRESTO was indicated for adult patients with HFrEF.
FDA, Food and Drug Administration; FL, Florida; OH, Ohio.

Q14: What effect does ENTRESTO® have on HF readmissions in patients with HFrEF?

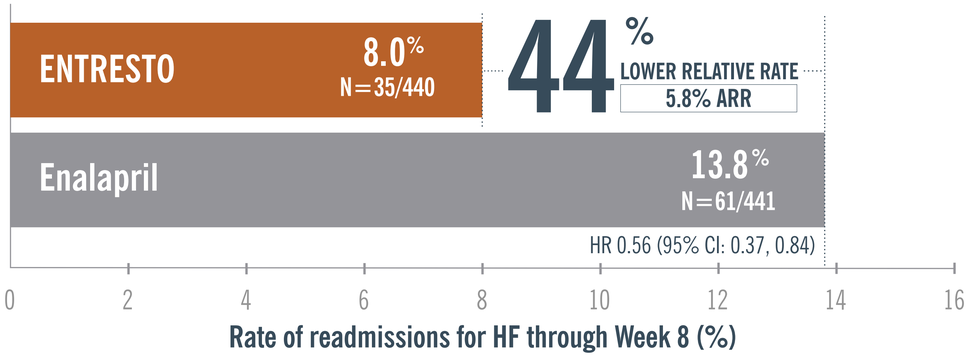
A: In PARADIGM-HF and PIONEER-HF,* ENTRESTO reduced HF readmissions† vs enalapril.[1,6,34]

In a post hoc analysis of PARADIGM-HF, HF readmissions were fewer with ENTRESTO at 30 days. ENTRESTO demonstrated a **38%** lower relative rate (OR 0.62 [95% CI: 0.45, 0.87] [3.7% ARR]) of 30-day HF readmission rates after HF hospitalization vs enalapril.[34]

When started in the hospital in stabilized patients, ENTRESTO reduced HF readmissions more than enalapril. In a prespecified exploratory end point of PIONEER-HF, ENTRESTO had a **44%** lower relative rate of readmissions compared to enalapril over 8 weeks (HR 0.56 [95% CI: 0.37, 0.84] [5.8% ARR]).[6]

PIONEER-HF: PRESPECIFIED EXPLORATORY END POINT

Inpatient initiation of ENTRESTO in stabilized patients resulted in fewer HF readmissions† over 8 weeks[6]



PARADIGM-HF HF readmissions analysis limitations: This as a post hoc analysis of HF readmissions following investigator-reported HF hospitalizations; investigator-reported events are vulnerable to misclassification. Patients were not randomized to treatment with ENTRESTO or enalapril at the time of index hospitalization; the apparent differences in readmission rate could be attributed to differences in the patients. The primary unit of subsequent analysis was hospitalizations rather than patients. **Definition of hospitalizations:** This analysis replicated the approach of the Hospital Readmissions Reduction Program, where all investigator-reported hospitalizations for HF were considered as potential index HF hospitalizations, not merely those that were adjudicated positively by the CEC.[34] **PIONEER-HF HF readmissions analysis limitations:** The study was powered for changes in NT-proBNP and secondary and exploratory end points should be interpreted with caution.[6]

*See Question 8 on page 13 for PARADIGM-HF study design and Question 10 on page 15 for the PIONEER-HF study design.

†In PIONEER-HF, readmission was defined as the first hospitalization after inpatient initiation of study drug. In PARADIGM-HF, readmission was defined as the second hospitalization within 30 days of the first hospitalization after initiation of study drug.[6,34]

CEC, Clinical Endpoints Committee.

IMPORTANT SAFETY INFORMATION (cont)

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

Click here for full Important Safety Information.

Click here for full Prescribing Information, including Boxed WARNING.

WHO is an appropriate patient for ENTRESTO?

Q15: In which types of patients has ENTRESTO been proven to be effective?

A: ENTRESTO is indicated to reduce the risk of CV death and hospitalization for HF in adult patients with chronic HF. Benefits are most clearly evident in patients with LVEF below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat.[1]

Whether in the outpatient or inpatient setting, you can start ENTRESTO across a wide range of newly and previously diagnosed patients with LVEF below normal.[9]

Please **click here** for full Prescribing Information, including **Boxed WARNING** and Contraindications, to determine if your patient is appropriate for ENTRESTO.

Q16: What range of ejection fraction can be considered below normal?

A: LVEF below normal can be defined as LVEF ≤60%. Approximately 80% of patients with HF have LVEF ≤60% and may be appropriate for ENTRESTO.[3,9]

The 2022 HF Guideline strongly recommends ENTRESTO in **HFrEF‡ (LVEF ≤40%)** to reduce morbidity and mortality and expands its recognition of ENTRESTO into 2 additional HF patient types: **HFmrEF with LVEF 41% to 49%** and **HFpEF with LVEF ≥50%** on the lower end of the spectrum.[9§]

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.[10]

‡NYHA Class II-III patients with HFrEF.

§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).

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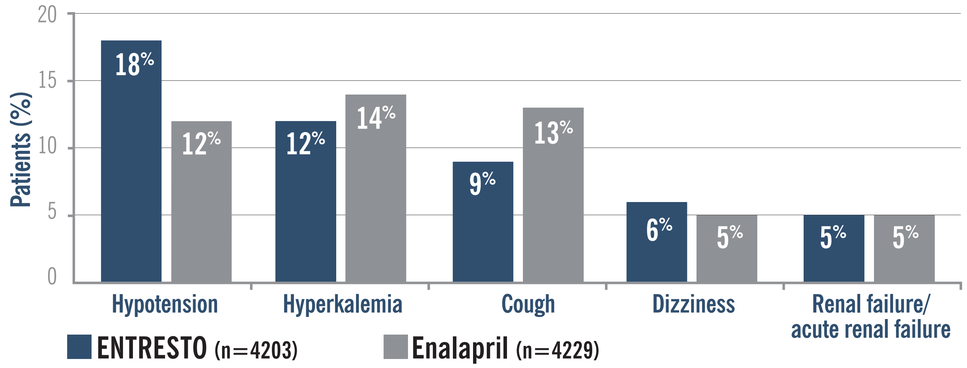
Q17: What is the safety profile of ENTRESTO®?

A: ENTRESTO has a proven safety profile comparable to an ACEi and an ARB.[1]

PARADIGM-HF: ENTRESTO HAS SAFETY COMPARABLE TO ENALAPRIL IN PATIENTS WITH HFrEF[1]*

Adverse reactions reported in ≥5% of patients treated with ENTRESTO in the double-blind period[6]*



*Due to the run-in period, adverse event rates were lower than would be expected in practice.

PARAGON-HF SAFETY PROFILE

No new safety signals were identified. Overall safety was comparable to an ARB.[1,4†]

†Due to the run-in period, adverse event rates were lower than would be expected in practice.

Event	ENTRESTO N=2407	Valsartan N=2389
Angioedema, n (%)	14 (0.6)	4 (0.2)
Elevated serum potassium		
>5.5 mmol/L, n/total (%)	316/2386 (13.2)	361/2367 (15.3)
>6.0 mmol/L, n/total (%)	75/2386 (3.1)	101/2367 (4.3)
Hypotension with SBP <100 mmHg, n (%)	380 (15.8)	257 (10.8)
Elevated serum creatinine, n (%)		
≥2.0 mg/dL	261 (10.8)	328 (13.7)
≥2.5 mg/dL	97 (4.0)	109 (4.6)
≥3.0 mg/dL	38 (1.6)	40 (1.7)

PIONEER-HF KEY SAFETY END POINTS

No significant differences were seen in rates of worsening renal function, hyperkalemia, symptomatic hypotension, or angioedema between ENTRESTO or enalapril.[6]

PARAGLIDE-HF 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).[8]

IMPORTANT SAFETY INFORMATION (cont)

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.

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

SBP, systolic blood pressure.

HOW do I manage treatment for patients on ENTRESTO®?

Q18: How do I start a patient on ENTRESTO after they have been stabilized in the hospital?

A: Once a patient is stabilized in the hospital, follow dosing instructions from the Prescribing Information. The starting dose of ENTRESTO is 24/26 mg or 49/51 mg BID, depending on the patient's current treatment. If the patient has been taking an ACEi, allow a washout period of 1.5 days (36 hours) before starting ENTRESTO. No washout is necessary if the patient has been taking an ARB. The dose of ENTRESTO should be doubled after 2 to 4 weeks to the target maintenance dose of 97/103 mg BID, as tolerated by the patient.[1]

IN THE PIONEER-HF TRIAL, HFrEF PATIENTS HOSPITALIZED FOR ADHF WERE CONSIDERED TO BE STABILIZED WHEN THEY MET ALL OF THE FOLLOWING CRITERIA[6]:

6 hours prior

- No increase (intensification) in IV diuretic dose
- No IV vasodilators, including nitrates
- SBP ≥100 mmHg
- No symptomatic hypotension

24 hours prior

- No IV inotropic drugs

THE MEDIAN TIME FOR PATIENTS TO MEET THE STABILIZATION CRITERIA WAS LESS THAN 3 DAYS AFTER INITIAL PRESENTATION TO THE HOSPITAL[6]

For detailed dosing instructions, **click here** for the full Prescribing Information, including **Boxed WARNING.**

Q19: Why is a 1.5-day (36-hour) washout period necessary before starting ENTRESTO if a patient is already taking an ACEi?

A: The short answer is that the washout period must be observed because of the increased risk of angioedema with concomitant use of ACEi and ENTRESTO.[1]

In addition to metabolizing natriuretic peptides, neprilysin, like ACE, is involved in the degradation of bradykinin. Therefore, the combination of neprilysin inhibition with ACE inhibition could increase the risk of bradykinin-mediated angioedema.[19,21,35]

ENTRESTO is contraindicated with concomitant use of ACEi. Do not administer within 1.5 days (36 hours) of switching from or to an ACEi. No washout is necessary if the patient has been taking an ARB.[1]

If ENTRESTO is appropriate:

FOR RASi-NAÏVE HF PATIENTS

Once your patients are stabilized, you can start them on ENTRESTO[6]

FOR HF PATIENTS ON AN ACEi

Plan for the switch

ENTRESTO requires a 36-hour (1.5 days) washout period before treatment initiation[1]

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.

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Q20: How should I dose ENTRESTO® in adult patients?

A: Choose initial dose of ENTRESTO, and after 2 to 4 weeks, titrate to the target dose, as tolerated by the patient.[1]

ENTRESTO IS AVAILABLE IN 3 DOSAGE STRENGTHS[1]:

Low Starting Dose	Recommended Starting Dose	Target Dose
24/26 mg BID	49/51 mg BID	97/103 mg BID

Pills shown not actual size.

- When switching from an ACEi, be sure to allow for a 1.5-day washout period prior to initiating ENTRESTO[1]
- When switching from an ARB, start ENTRESTO at your patients' next scheduled dose[1]
  - ENTRESTO is contraindicated with concomitant use of an ACEi and in patients with a history of angioedema related to previous ACEi or ARB therapy
  - Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker

The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.[1]

SWITCHING FROM A LOWER DOSE OR NOT CURRENTLY ON AN ACEi OR ARB[1]:

Low-dose ACEi	**STOP ACEi** **Wait** 36 hours then switch to ENTRESTO	**STARTING DOSE** 24/26 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO** 49/51 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO TARGET DOSE** 97/103 mg twice daily, as tolerated by the patient
Low-dose ARB or no ACEi/ARB	**STOP ARB** **GO** Switch to ENTRESTO			

- **Low-dose ACEi:** total daily dose of ≤10 mg of enalapril or therapeutically equivalent dose of another ACEi (eg, lisinopril ≤10 mg; ramipril ≤5 mg)
- **Low-dose ARB:** total daily dose of ≤160 mg valsartan or therapeutically equivalent dose of another ARB (eg, losartan ≤50 mg; olmesartan ≤10 mg)

SWITCHING FROM A HIGHER DOSE OF AN ACEi OR ARB[1]:

High-dose ACEi	**STOP ACEi** **Wait** 36 hours then switch to ENTRESTO	**STARTING DOSE** 49/51 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO TARGET DOSE** 97/103 mg twice daily, as tolerated by the patient
High-dose ARB	**STOP ARB** **GO** Switch to ENTRESTO		

- **High-dose ACEi:** total daily dose of >10 mg of enalapril or therapeutically equivalent dose of another ACEi (eg, lisinopril >10 mg; ramipril >5 mg)
- **High-dose ARB:** total daily dose of >160 mg valsartan or therapeutically equivalent dose of another ARB (eg, losartan >50 mg; olmesartan >10 mg)

A 1.5-DAY WASHOUT IS NOT REQUIRED FOR PATIENTS SWITCHING FROM AN ARB TO ENTRESTO.

For complete dosage and administration, always refer to the full Prescribing Information.

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**

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

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Q21: How do I initiate ENTRESTO® in patients with renal impairment?

A: There is no contraindication for patients with renal impairment.

- **No starting dose adjustment** is required in patients with **mild** (eGFR 60 to 90 mL/min/1.73 m^2) to **moderate** (eGFR 30 to 60 mL/min/1.73 m^2) renal impairment
- The recommended starting dose in patients with **severe** renal impairment (eGFR <30 mL/min/1.73 m^2) is 24/26 mg twice daily, which is half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter[1]

Q22: How do I treat a patient who develops angioedema while on ENTRESTO?

A: IMPORTANT ANGIOEDEMA SAFETY INFORMATION

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. Patients with a prior history of angioedema may be at an increased risk of angioedema with ENTRESTO. ENTRESTO must not be used in patients with a known history of angioedema related to previous ACEi or ARB therapy. ENTRESTO should not be used in patients with hereditary angioedema.[1]

If angioedema occurs[1]:

- Discontinue ENTRESTO immediately
- Provide appropriate therapy
- Monitor for airway compromise
- ENTRESTO must not be re-administered

Q23: How do I treat a patient who becomes hypotensive while taking ENTRESTO?

A: IMPORTANT HYPOTENSION SAFETY INFORMATION

ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated RAAS, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), are at greater risk.[1]

As detailed in the table below, hypotension was a commonly reported adverse event during the double-blind period of the PARADIGM-HF trial.[1,5]*

	ENTRESTO (n=4203)	Enalapril (n=4229)
Hypotension[1]	18%	12%
Treatment discontinuation due to hypotension[5]	0.9%	0.7%

To address hypotension[1]:

- Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose
- If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (eg, hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue ENTRESTO
- Permanent discontinuation of therapy is usually not required

eGFR, estimated glomerular filtration rate.

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.

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

*Due to the run-in design of the PARADIGM-HF study, adverse event rates were lower than would be expected in practice.

Q24: How do I treat a patient who experiences renal impairment while taking ENTRESTO®?

A: IMPORTANT IMPAIRED RENAL FUNCTION SAFETY INFORMATION

In susceptible individuals treated with ENTRESTO, decreases in renal function may be anticipated as a consequence of inhibiting RAAS. In patients whose renal function depends upon the activity of the RAAS (eg, 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.[1]

To manage renal function:

- When initiating RAS inhibition with ENTRESTO, closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function[1]

In a broad range of patients with HF, ENTRESTO has demonstrated a consistent renal safety profile.[5,6,36]

PARADIGM-HF renal safety profile

Renal impairment was rarely the cause of stopping study medication in patients with HFrEF.[5,37]

- Fewer patients in the ENTRESTO group (0.7%) stopped their study medication permanently because of renal impairment than in the enalapril group (1.4%)[5]
- Serum creatinine levels of 2.5 mg/dL (221 μmol/L) or more were reported less frequently in the ENTRESTO group (3.3%) than in the enalapril group (4.5%)[5]

PARAGON-HF renal safety profile

Rates of renal impairment were similar to valsartan in patients with HFpEF* with an LVEF $\leq$57%.[35†]

- Rates[‡] of renal adverse events were similar to that of the valsartan (ARB) active comparator in the subgroup of patients with LVEF at or below the median (57%)[37]
  - Renal impairment: 11.5% vs 15.4%
  - AKI: 5.3% vs 5.4%
  - Renal failure: 3.9% vs 5.2%

Q25: How do I treat a patient if hyperkalemia occurs while taking ENTRESTO?

A: IMPORTANT HYPERKALEMIA SAFETY INFORMATION

Through its actions on the RAAS, hyperkalemia may occur with ENTRESTO. Concomitant use of ENTRESTO and potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to an increase in serum potassium levels.[1]

The table below details the rates of hyperkalemia during the double-blind period of the PARADIGM-HF trial.[1,5§]

	ENTRESTO (n=4203)	Enalapril (n=4229)
Hyperkalemia[1]	12%	14%
Treatment discontinuation due to hyperkalemia[5]	0.3%	0.4%

To address hyperkalemia[1]:

- 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

*The patient population of PARAGON-HF met the protocol definition of HFpEF with an LVEF $\geq$45%, structural heart disease (either LAE or LVH), and no prior echocardiographic LVEF <40%.
†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.
‡A patient with multiple instances of an AE is counted once.

AE, adverse event; AKI, acute kidney injury.

§Due to the run-in design of the PARADIGM-HF study, adverse event rates were lower than would be expected in practice.[1]

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.

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

Q26: How does Novartis provide support when patients need ENTRESTO®?

A: ENTRESTO supports your eligible HF patients with options to help them start and stay on treatment.

FOR PATIENTS WITH MEDICARE

ENTRESTO is available at the lowest branded co-pay for more than 99% of eligible patients[38]

THE ENSPIRE PROGRAM FROM ENTRESTO®*

Your patients can sign up for this 12-month lifestyle and treatment support program† where a dedicated ENTRESTO Support Specialist will provide personalized one-on-one support throughout their treatment journey

FOR ELIGIBLE COMMERCIALLY INSURED PATIENTS

May pay as little as a $10 co-pay for up to a 90-day supply of ENTRESTO‡

AVAILABLE TO ALL PATIENTS§:

Regardless of insurance, patients can access a 30-day free trial offer, pre-activated and ready to use when initiating treatment.

*Must be 18 or older to enroll in the ENSPIRE Program from ENTRESTO®.

†Your patient can choose how they would like to be contacted, and they can opt out of any of these communications at any time.

‡Limitations apply. See Program Terms and Conditions. Eligible commercial patients pay as little as a $10 co-pay for each prescription fill (30-, 60-, 90-day fill) at retail or mail order. The program pays up to a $4100 cap across all fills per calendar year. Patient will be responsible for any co-pay once the $4100 limit is reached in a calendar year. This offer is not valid under Medicare, Medicaid, or any other federal or state program. See complete Terms and Conditions for details at EntrestoHCP.com/support-and-resources.

§Limitations apply. This voucher is good for a 30-day (maximum 60 tablets; **one-time use**) free trial of ENTRESTO at no cost for your patient. Visit EntrestoHCP.com/support-and-resources to view Terms and Conditions.

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.

Click here for full Important Safety Information.
Click here for full Prescribing Information, including Boxed WARNING.

ENTRESTO COVERAGE

With comprehensive information on health plan coverage, PA requirements, and PA forms, helping your patients get access to ENTRESTO is as easy as 1, 2, 3. For more information, visit **entresto-coverage.com**.

For information on regional ENTRESTO coverage, contact your local sales representative, who may be able to provide more information.

FOR YOUR PATIENTS WITH LIMITED OR NO PRESCRIPTION COVERAGE, THEY MAY QUALIFY FOR HELP FROM NOVARTIS PATIENT ASSISTANCE FOUNDATION (NPAF)

NPAF, a nonprofit organization, is committed to providing access to Novartis medications for those most in need. If your patient is experiencing financial hardship, has limited or no prescription coverage, and cannot afford the cost of their medications, then they may be eligible to receive Novartis medications for free. To learn more, call 1-800-277-2254 or visit **www.PAP.Novartis.com**.

FOR INFORMATION ON ENTRESTO SUPPORT AND RESOURCES

Start Early. Start Now. Start ENTRESTO.

PA, prior authorization.

Entresto® (sacubitril/valsartan) tablets
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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.

Click here for full Prescribing Information, including Boxed WARNING.

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IN MOST PATIENTS WITH HEART FAILURE– HELP HEART FAILURE MEET HEART SUCCESS WITH ENTRESTO®

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