# Deep Dive- ARNI trials

**Objectives:**

- Provide an outline of the sacubutril-Valsartan clinical trials
- Understand mechanism of action of sacubutril-valsartan
- Deep dive –PARADIGM HF, PIONEER HF

# Disclaimer

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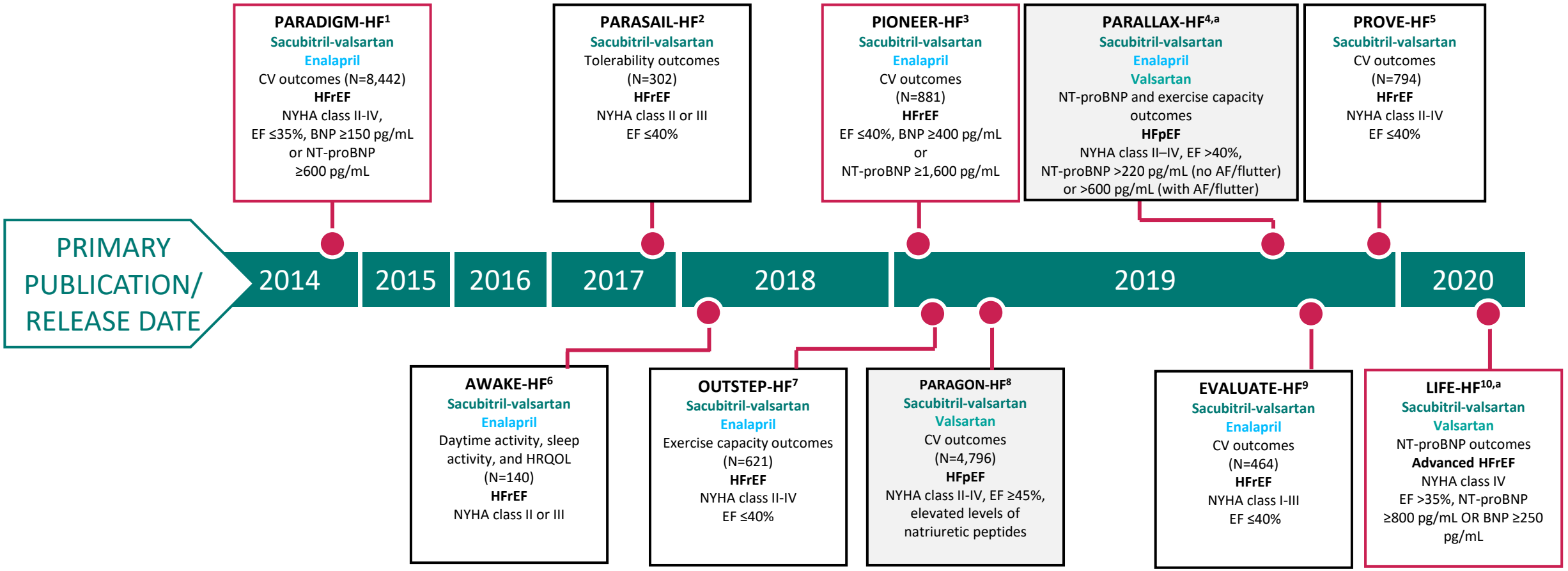
# ENTRESTO® (sacubitril/valsartan) CLINICAL COMPENDIUM

MA-M_VER-ALL-0042-1

# PUBLISHED SACUBITRIL-VALSARTAN CLINICAL TRIALS IN HF

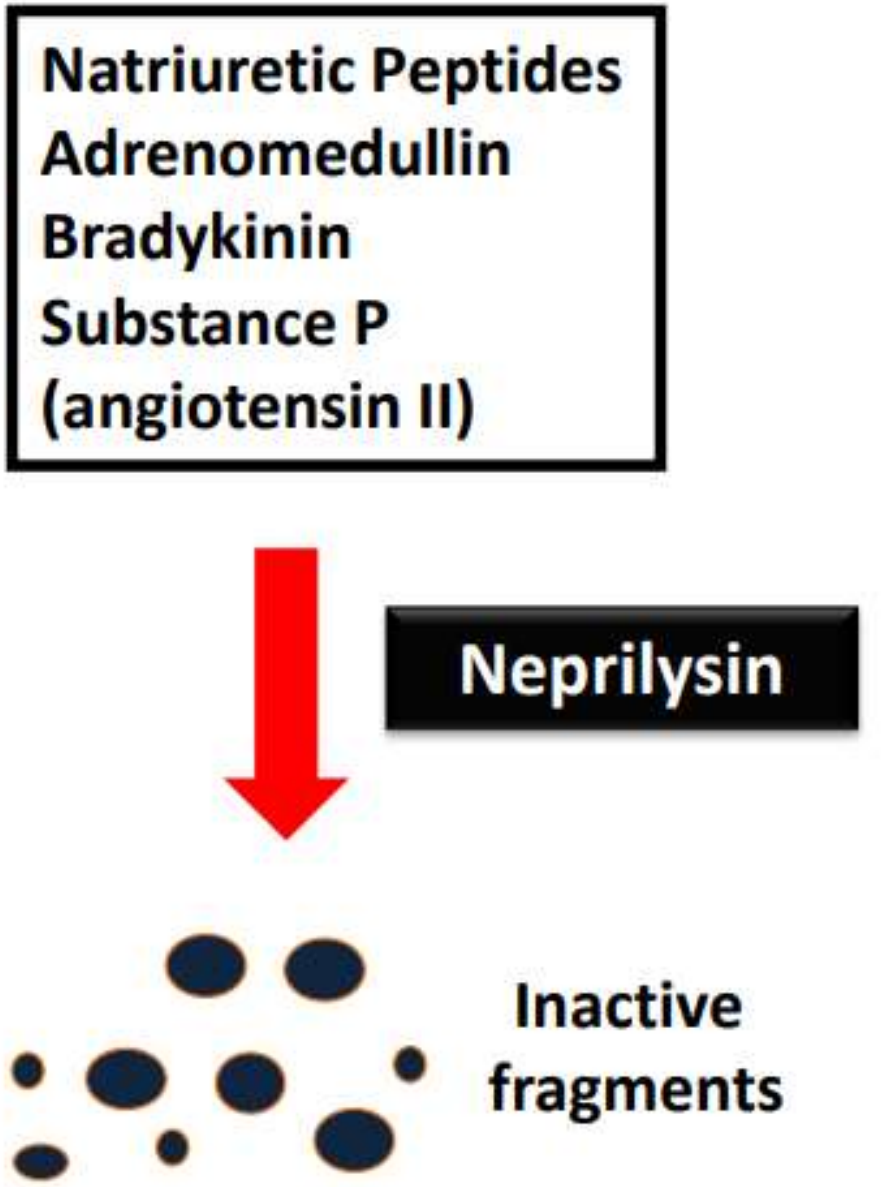



Information provided for each trial includes primary outcomes, patient population, and selected CV selection criteria.

[a]Data pending publication.

AF= atrial fibrillation; BNP = brain natriuretic peptide; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HRQOL = health-related quality of life; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

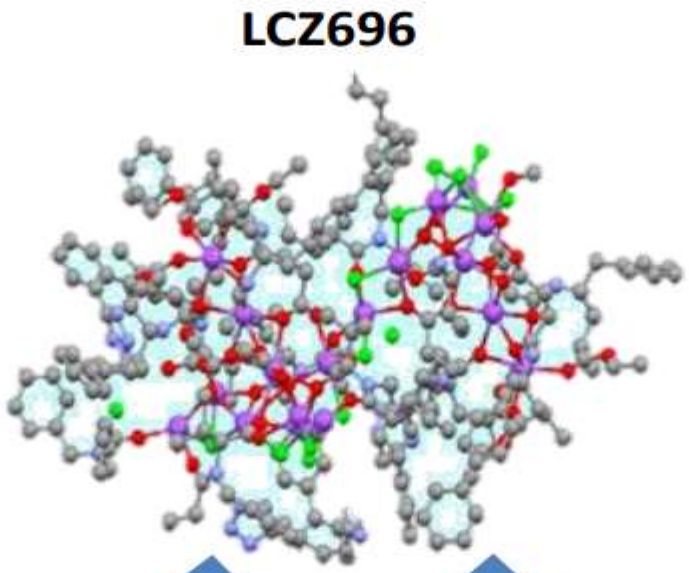
**1.** McMurray JJ et al. *N Engl J Med*. 2014;371:993–1004. **2.** NCT02690974. ClinicalTrials.gov Web site. clinicaltrials.gov/ct2/show/results/NCT02690974. Accessed August 13, 2020. **3.** Velazquez EJ et al. *N Engl J Med*. 2019;380:539–548. **4.** Wachter R et al. *ESC Heart Fail*. 2020;7:856–864. **5.** Januzzi JL Jr et al. *JAMA*. 2019;322:1085–1095. **6.** NCT02970669. ClinicalTrials.gov Web site. clinicaltrials.gov/ct2/show/results/NCT02970669?term=AWAKE&cond=heart+failure&draw=1&rank=1&view=results. Accessed August 13, 2020. **7.** NCT02900378. ClinicalTrials.gov Web site. clinicaltrials.gov/ct2/show/results/NCT02900378. Accessed August 13, 2020. **8.** Solomon SD et al. *N Engl J Med*. 2019;381:1609–1620. **9.** Desai AS et al. *JAMA*. 2019;322:1077–1084. **10.** NCT02816736. ClinicalTrials.gov Web site. clinicaltrials.gov/ct2/show/NCT02816736. Accessed August 13, 2020.




# Neprilysin as a therapeutic target

- Neprilysin is responsible for the breakdown of a number of endogenous vasoactive peptides, including the natriuretic peptides
- Inhibition of neprilysin potentiates the action of those peptides
- Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors must be coadministered with a RAAS blocker
- The combination of a neprilysin inhibitor and an ACE-inhibitor is associated with unacceptably high rates of angioedema

# Sacubitril/Valsartan (LCZ696): A first-in-class angiotensin/neprilysin inhibitor (ARNi)




LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio

Dissociates at low pH

**Sacubitril**

↓

**LBQ657**

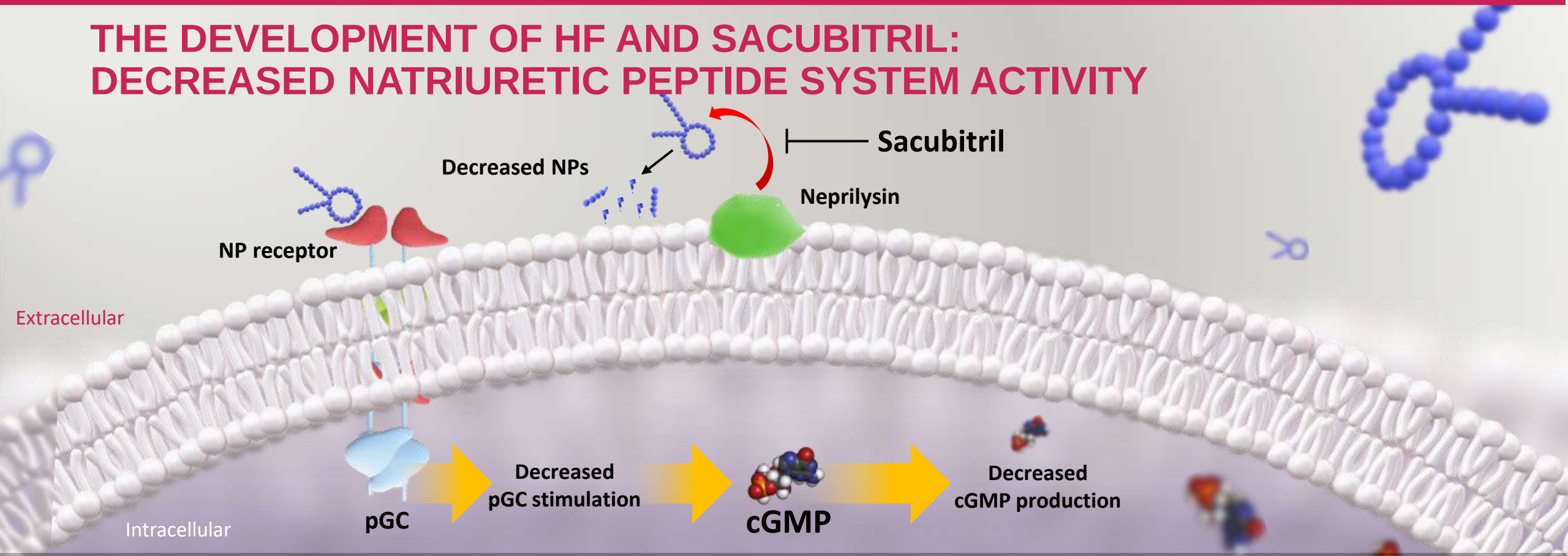
Neprilysin Inhibitor

+

**Valsartan**

ARB

# THE DEVELOPMENT OF HF AND SACUBITRIL: DECREASED NATRIURETIC PEPTIDE SYSTEM ACTIVITY

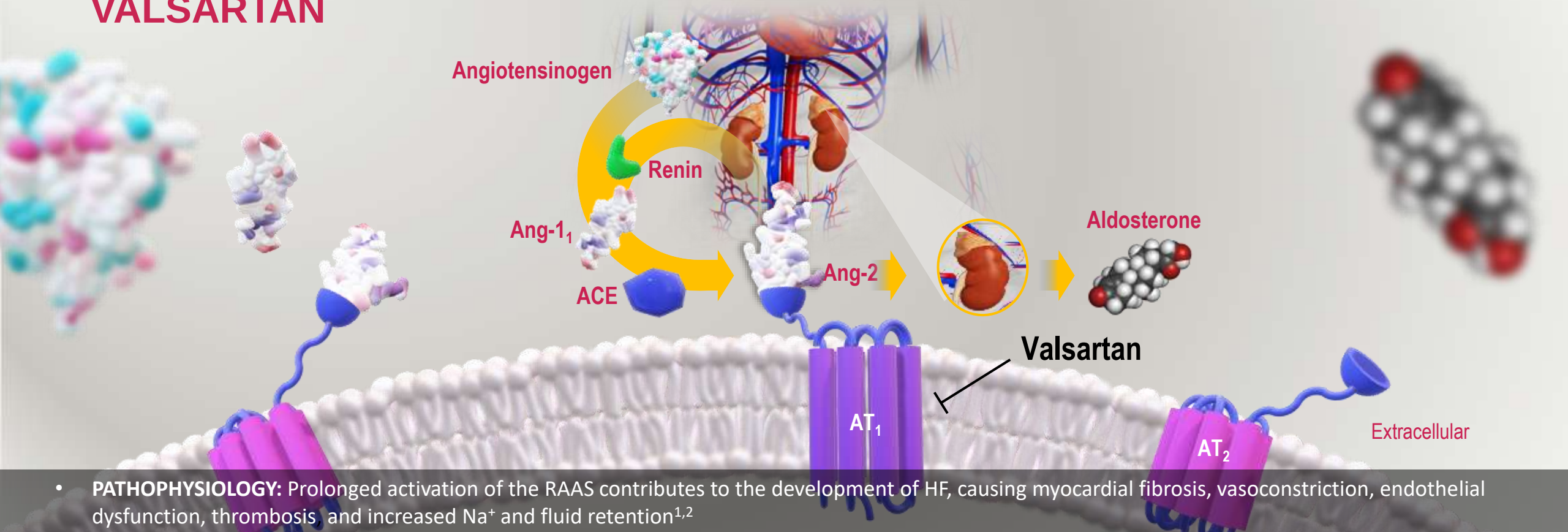



- **PATHOPHYSIOLOGY:** Prolonged activation of the SNS and RAAS facilitates the increased release of NPs to counter-regulate worsening HF; as HF progresses NPs may degraded by neprilysin[1–3]
- **MECHANISM OF ACTION:** Sacubitril's active metabolite inhibits neprilysin, an endopeptidase that degrades NPs[3]
- **CLINICAL EFFECT:** Sacubitril enhances the helpful, counterregulatory NP system; this increases vasodilation, reduces hypertrophy and fibrosis, and increases $Na^+$ and fluid excretion[4]

cGMP = cyclic guanosine monophosphate; HF = heart failure; $Na^+$ = sodium; pGC = particulate guanylate cyclase; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

**1.** Felker GM et al. *Heart Failure*. 4th ed. Elsevier; 2020. **2.** Liu RC. *Am J Cardiovasc Drugs*. 2018;18:473–482. **3.** Entresto [package insert]. Kenilworth, NJ: Merck Pharmaceuticals, Inc. 2020. **4.** ENTRESTO is a unique combination of valsartan PLUS sacubitril, a neprilysin inhibitor. Entresto website. www.entrestohcp.com/mechanism-of-action. Accessed August 13, 2020.

# EFFECTS OF RAAS ACTIVATION, THE DEVELOPMENT OF HF, AND VALSARTAN




- **PATHOPHYSIOLOGY:** Prolonged activation of the RAAS contributes to the development of HF, causing myocardial fibrosis, vasoconstriction, endothelial dysfunction, thrombosis, and increased $Na^+$ and fluid retention[1,2]
- **MECHANISM OF ACTION:** Valsartan inhibits the effects of Ang-2 by selectively blocking the $AT_1$ receptor and by inhibiting Ang-2–dependent aldosterone release[3]
- **CLINICAL EFFECT:** Valsartan inhibits the harmful effects of overactivated RAAS; this decreases vasoconstriction, reduces hypertrophy and fibrosis, and increases $Na^+$ and fluid excretion[4]

ACE = angiotensin-converting enzyme; Ang = angiotensin; AT = angiotensin; HF = heart failure; $Na^+$ = sodium; RAAS = renin-angiotensin-aldosterone system.

**1.** Capote L et al. In: Jagadeesh G. *Pathophysiology and Pharmacotherapy of Cardiovascular Disease*. Springer International Publishing Switzerland; 2015:37–55. **2.** Mentz RJ et al. *Int J Cardiol*. 2013;167:1677–1687. **3.** Entresto [package insert]. Kenilworth, NJ: Merck Pharmaceuticals, Inc. 2020. **4.** ENTRESTO is a unique combination of valsartan PLUS sacubitril, a neprilysin inhibitor. Entresto website. www.entrestohcp.com/mechanism-of-action. Accessed August 13, 2020.

# CLINICAL SUPPORT FOR THE USE OF SACUBITRIL-VALSARTAN

## Clinical Outcomes

**PARADIGM-HF[a]**
- Decreased risk of HFH, CV death, and all-cause death

**PIONEER-HF[a]**
- Decreased risk of HFH and CV death

## Patient Experience

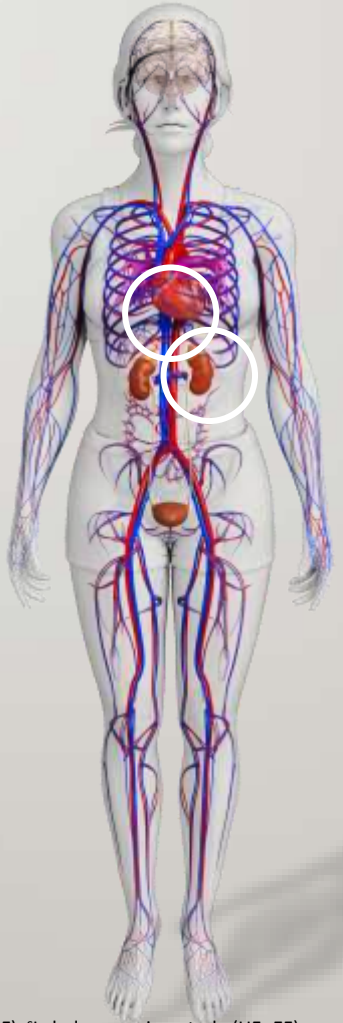
**PARADIGM-HF[a]**
- Improved KCCQ

**EVALUATE-HF[b]**
- Improved KCCQ scores

**OUTSTEP-HF[b]**
- Improved 6MWT

**AWAKE-HF[b]**
- Improved sleep quality

**PARASAIL-HF[b]**
- Improved PGA
- Improved MLHFQ
- Improved 6MWT



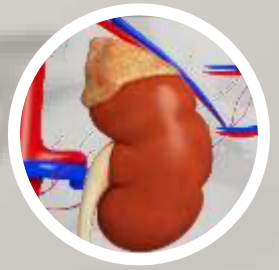
## Tissue/Organ Structure and Function/Performance

**PIONEER-HF[a]**
- Decreased NT-proBNP
- Reduced sST2
- Reduced hsTnT

**PROVE-HF[b]**
- Increased EF
- Improved LVEDVI
- Improved LVESVI
- Improved LAVI
- Improved E/e'
- Decreased NT-proBNP

**EVALUATE-HF[b]**
- Decreased NT-proBNP
- Reduced sST2
- Reduced hsTnT
- Improved LAVI
- Improved LVESVI
- Improved LVEDVI

**PARALLAX (*In progress*)[c]**
- NT-proBNP



**PARADIGM-HF[a]**
- Improved eGFR

## Molecular/Cellular

**PIONEER-HF[a]**
- Increased urinary cGMP

**EVALUATE-HF[b]**
- Increased urinary cGMP

[a]Landmark study (HFrEF); [b] Label-supporting study (HFrEF); [c]Label-expansion study (HFpEF)

6MWT = 6-minute walking test; AT = angiotensin; CV = cardiovascular; cGMP = cyclic guanosine monophosphate; E/e' = ratio of early transmitral Doppler velocity/early diastolic annular velocity; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESVI = end-systolic volume index; HF = heart failure; HFH= heart failure hospitalization; hsTnT = high-sensitivity troponin T; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; MLHFQ = Minnesota LIVING WITH HEART FAILURE; NT-proBNP = N-terminal pro-brain natriuretic peptide; PGA = patient global assessment; QOL = quality of life; RAAS = renin-angiotensin-aldosterone system; sST2 = soluble suppression of tumorigenesis-2.

# EU SUMMARY OF PRODUCT CHARACTERISTICS[1]

## 1. NAME OF THE MEDICINAL PRODUCT

Entresto 24 mg/26 mg film-coated tablets
Entresto 49 mg/51 mg film-coated tablets
Entresto 97 mg/103 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Entresto 24 mg/26 mg film-coated tablets

Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).

Entresto 49 mg/51 mg film-coated tablets

Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).

Entresto 97 mg/103 mg film-coated tablets

Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).

# Therapeutic indications

- Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction

## 4.2 Posology and method of administration

Posology

The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient (see section 5.1).

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Entresto is recommended (see section 4.4).

In PARADIGM-HF study, Entresto was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other angiotensin II receptor blocker (ARB) (see section 5.1). There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, therefore a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients (see "Titration" in section 5.1).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section 4.4). A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

Entresto should not be co-administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see sections 4.3, 4.4 and 4.5).

*Renal impairment*

No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 $m^2$) renal impairment. A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 $m^2$). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 $m^2$) (see section 5.1) Entresto should be used with caution and a starting dose of 24 mg/26 mg twice daily is recommended. There is no experience in patients with end-stage renal disease and use of Entresto is not recommended.

## 4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors (see sections 4.4 and 4.5). Entresto must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy (see section 4.4).
- Hereditary or idiopathic angioedema (see section 4.4).
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 $m^2$) (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 4.2).
- Second and third trimesters of pregnancy (see section 4.6).

Impaired renal function

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m$^2$) and these patients may be at greatest risk of hypotension (see section 4.2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.

Worsening renal function

Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) (see section 4.5). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists (see section 4.2). If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.

# LANDMARK CLINICAL STUDIES

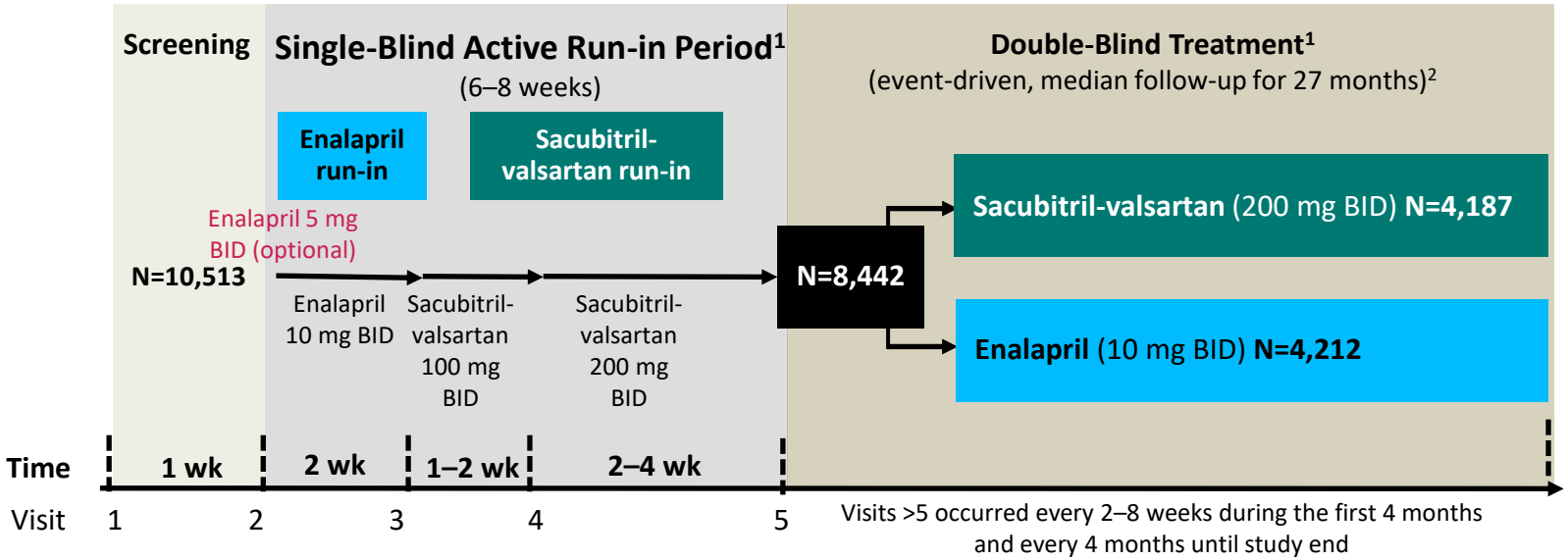
Studies supporting the use of sacubitril-valsartan in patients with chronic and acutely decompensated HFrEF

- PARADIGM-HF (Phase 3)
- PIONEER-HF (Phase 3)

# PARADIGM-HF

**A Phase 3 Clinical Trial in 8,442 Patients With Chronic HFrEF**

# PARADIGM-HF: STUDY DESIGN AND KEY STUDY OUTCOMES




**Study to evaluate the effect of sacubitril-valsartan compared with enalapril on morbidity and mortality in patients with chronic HF[2]**

## Primary Outcome[2]

The composite of death from CV causes or a first HFH

## Selected Secondary Outcomes[2]

- Time to death from any cause
- Change in KCCQ from baseline to 8 months
- Time to new onset of atrial fibrillation
- Time to first occurrence of a decline in renal function[a]

## Selected Exploratory Outcomes[1]

- Time to first occurrence of a composite of CV death, HFH, nonfatal MI, nonfatal stroke, or resuscitated sudden death
- Number of patients hospitalized and number of hospital admissions (all-cause and cause-specific)
- Days alive out of hospital at 12 months
- Rate of decline in eGFR
- Time to treatment failure

The study was powered to detect a relative reduction of 15% in the risk of death from CV causes in the sacubitril-valsartan group.[1]

[a]Defined as end-stage renal disease or a decrease in the eGFR ≤50% or a decrease ≥30 mL/mi/1.73 m$^2$ from randomization to <60 mL/min/1.73 m$^2$.

BID = twice daily; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFH = heart failure hospitalization; KCCQ = Kansas City Cardiomyopathy Questionnaire; MI = myocardial infarction.

**1.** McMurray JJ et al. *Eur J Heart Fail.* 2013;15:1062–1073. **2.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

# PARADIGM-HF: BASELINE CHARACTISTICS AND ELIGIBILITY CRITERIA

## Selected Inclusion Criteria[1]

- Age ≥18 years
- NYHA functional class II–IV
- LVEF ≤35%
- Plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL) at screening OR BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) and HFH within the last 12 months
- Stable treatment with an ACEi or an ARB equivalent to enalapril 10 mg/d for ≥4 weeks before screening
- Stable treatment with a β-blocker for ≥4 weeks prior to screening, unless contraindicated or not tolerated

## Selected Exclusion Criteria[1]

- History of angioedema
- Acute decompensated HF
- eGFR <30 mL/min/1.73 $m^2$ at screening, Visit 3 or 5
- Acute coronary syndrome, CV incident, major CV surgery, PCI, or carotid angioplasty ≤3 months prior to screening

**Selected Baseline Characteristics in PARADIGM-HF[2,a]**

| Characteristic | Sacubitril-valsartan (n=4,187) | Enalapril (N=4,212) |
|---|---|---|
| **Age – y** | 63.8 ± 11.5 | 63.8 ± 11.3 |
| **Female – no. (%)** | 879 (21.0) | 953 (22.6) |
| **Race or ethnic group – no. (%)[b]** | | |
| White | 2,763 (66.0) | 2,781 (66.0) |
| Black | 213 (5.1) | 215 (5.1) |
| Asian | 759 (18.1) | 750 (17.8) |
| Other | 452 (10.8) | 466 (11.1) |
| **Systolic blood pressure – mm Hg** | 122 ± 15 | 121 ± 15 |
| **Heart rate – beats/min** | 72 ± 12 | 73 ± 12 |
| **Body-mass index[c]** | 28.1 ± 5.5 | 28.2 ± 5.5 |
| **Serum creatinine – mg/dL** | 1.13 ± 0.3 | 1.12 ± 0.3 |
| **Clinical features of HF** | | |
| Ischemic cardiomyopathy – no. (%) | 2,506 (59.9) | 2,530 (60.1) |
| LVEF – % | 29.6 ± 6.1 | 29.4 ± 6.3 |
| Median BNP (IQR) – pg/mL | 255 (155–474) | 251 (153–465) |
| Median NT-proBNP (IQR) – pg/mL | 1,631 (885–3154) | 1,594 (886–3,305) |
| **NYHA functional class – no. (%)[d]** | | |
| I | 180 (4.3) | 209 (5.0) |
| II | 2,998 (71.6) | 2,921 (69.3) |
| III | 969 (23.1) | 1,049 (24.9) |
| IV | 33 (0.8) | 27 (0.6) |
| **Medical history — no. (%)** | | |
| Hypertension | 2,969 (70.9) | 2,971 (70.5) |
| Diabetes | 1,451 (34.7) | 1,456 (34.6) |
| Atrial fibrillation | 1,517 (36.2) | 1,574 (37.4) |
| HFH | 2,607 (62.3) | 2,667 (63.3) |
| Myocardial infarction | 1,818 (43.4) | 1,816 (43.1) |
| Stroke | 355 (8.5) | 370 (8.8) |
| Pretrial use of ACEi[e] | 3,266 (78.0) | 3,266 (77.5) |
| Pretrial use of ARB[e] | 929 (22.2) | 963 (22.9) |
| **Treatments at randomization – no. (%)** | | |
| Diuretic | 3,363 (80.3) | 3,375 (80.1) |
| Digitalis | 1,223 (29.2) | 1,316 (31.2) |
| β-blocker | 3,899 (93.1) | 3,912 (92.9) |
| Mineralocorticoid antagonist | 2,271 (54.2) | 2,400 (57.0) |
| Implantable cardioverter–defibrillator | 623 (14.9) | 620 (14.7) |
| Cardiac resynchronization therapy | 292 (7.0) | 282 (6.7) |

[a]Plus–minus values are means ±SD; [b] Race or ethnic group was reported by the investigators; [c] The body-mass index is the weight in kilograms divided by the square of the height in meters; [d]NYHA class reflects the status at randomization. Patients were required to have at least NYHA class II symptoms at screening while 13 patients had no/missing NYHA data. [e]At the screening visit, 20 patients were not receiving the protocol-required treatment with an ACE inhibitor or an ARB, and 45 patients were taking both drugs.
ACEi = angiotensin-converting enyme inhibitor; ARB = angiotensin II receptor blocker; BNP = B-type natriuretic peptide; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFH = heart failure hospitalization; IQR = interquartile range; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SD = standard deviation.
**1.** McMurray JJ et al. *Eur J Heart Fail.* 2013;15:1062–1073. **2.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

# PARADIGM-HF: PRIMARY OUTCOME—COMPOSITE END POINT[1]

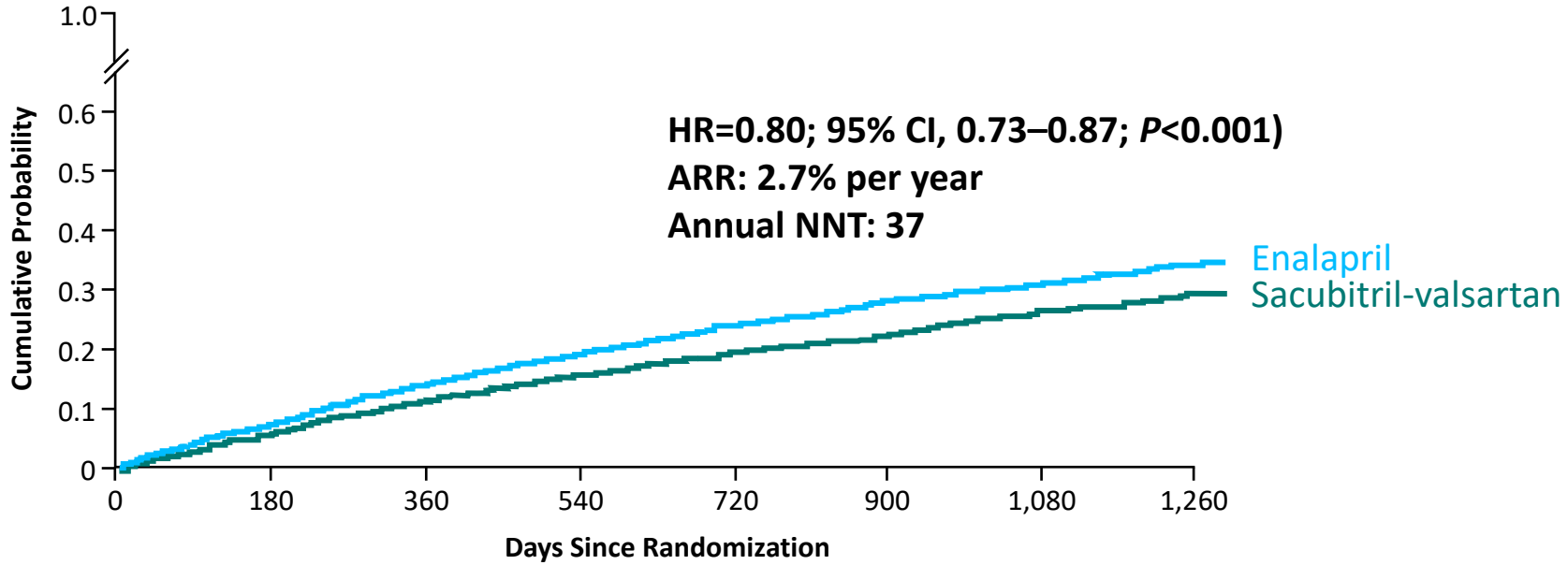
**Treatment with sacubitril-valsartan significantly reduced the risk of the primary composite end point of HFH or CV death (*P*<0.001).**

In the VICTORIA study, vericiguat significantly reduced the risk of the composite of HFH and CV death.

- HR=0.90; 95% CI, 0.82–0.98; *P*=0.02
- ARR: 4.2% per year
- Annual NNT: 24

**Reference**
Armstrong PW et al. *N. Engl J Med.* 2020; 382:1883–1893

**Primary End Point**




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sacubitril-valsartan | 4,187 | 3,922 | 3,663 | 3,018 | 2,257 | 1,544 | 896 | 249 |
| Enalapril | 4,212 | 3,883 | 3,579 | 2,922 | 2,123 | 1,488 | 853 | 236 |

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HFH = heart failure hospitalization; HR = hazard ratio; NNT = number needed to treat.

**1.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

# PARADIGM-HF: SECONDARY OUTCOMES[1]

**The primary outcomes of CV death and HFH, and the secondary outcom significant (*P*<0.001).**

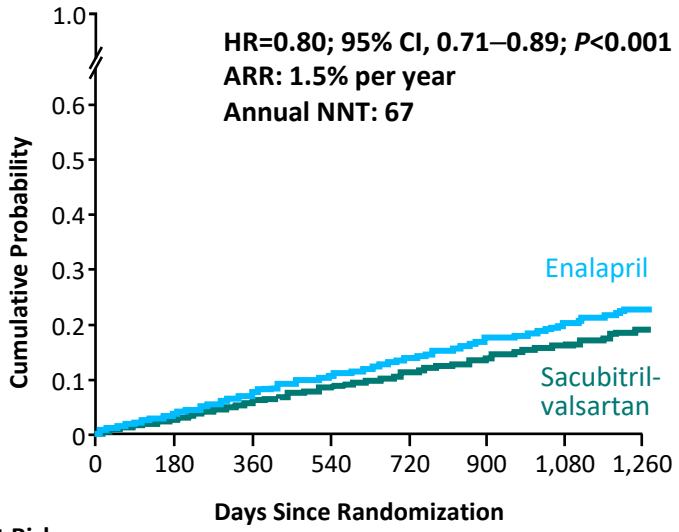
In the VICTORIA study vericiguat significantly reduced the risk of HFH, but did not significantly reduce the risk of CV death or all-cause death.

- CV death: HR=0.93; 95% CI, 0.81–1.06; *P*=0.269; ARR=1.0% per year; Annual NNT = 100
- First HFH: HR=0.90; 95% CI, 0.81–1.00; *P*=0.048; ARR=3.2% per year; Annual NNT=31
- All-cause death: HR=0.95; 95% CI, 0.84–1.07; *P*=0.377; ARR=0.9%; Annual NNT = 112

**Reference**

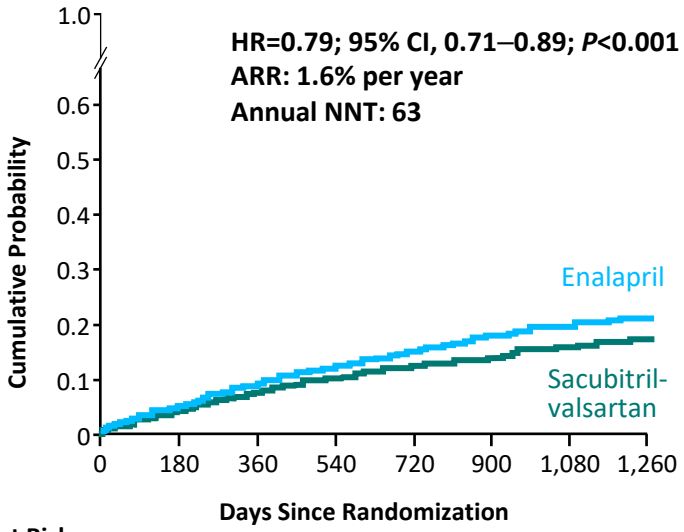
Merck Sharp & Dohme Corp. Data on file; Bayer AG. Data on file.

**Death From CV Causes**



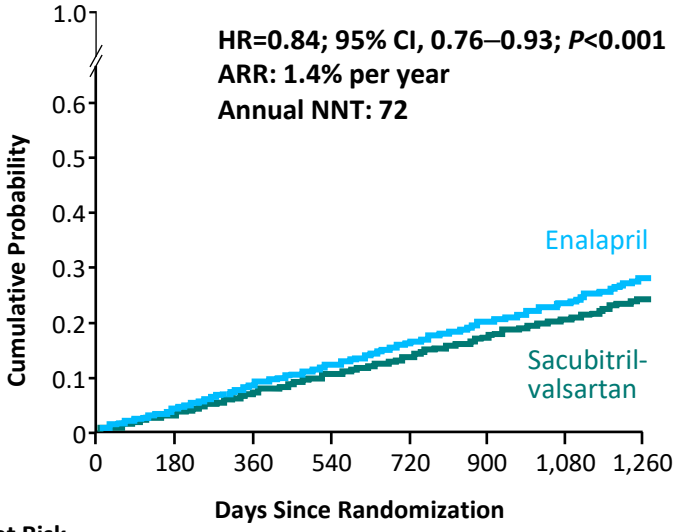

| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sacubitril-valsartan | 4,187 | 4,056 | 3,891 | 3,282 | 2,478 | 1,716 | 1,005 | 280 |
| Enalapril | 4,212 | 4,051 | 3,860 | 3,231 | 2,410 | 1,726 | 994 | 279 |

**HFH**




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sacubitril-valsartan | 4,187 | 3,922 | 3,663 | 3,018 | 2,257 | 1,544 | 896 | 249 |
| Enalapril | 4,212 | 3,883 | 3,579 | 2,922 | 2,123 | 1,488 | 853 | 236 |

**Death From Any Cause**




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sacubitril-valsartan | 4,187 | 4,056 | 3,891 | 3,282 | 2,478 | 1,716 | 1,005 | 280 |
| Enalapril | 4,212 | 4,051 | 3,860 | 3,231 | 2,410 | 1,726 | 994 | 279 |

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HFH = heart failure hospitalization; HR = hazard ratio; NNT = number needed to treat.

**1.** McMurray JJ et al. *N Engl J Med*. 2014;371:993–1004.

# PARADIGM-HF: PRIMARY AND SECONDARY OUTCOMES–QOL[1]

- **Sacubitril-valsartan retained patient quality of life significantly more than enalapril did (*P*=0.001)**
  - Reduction in the mean KCCQ summary score from baseline to month 8 was -2.99 points in the sacubitril-valsartan group vs –4.63 points in the enalapril group

| Outcome[a] | Sacubitril-Valsartan (N=4,187) | Enalapril (N=4,212) | Hazard Ratio or Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| **Primary composite outcome, no. (%)** | | | | |
| CV death or first HFH for worsening HF | 914 (21.8) | 1,117 (26.5) | 0.80 (0.73–0.87) | <0.001 |
| CV death | 558 (13.3) | 693 (16.5) | 0.80 (0.71–0.89) | <0.001 |
| First HFH for worsening HF | 537 (12.8) | 658 (15.6) | 0.79 (0.71–0.89) | <0.001 |
| **Secondary outcomes, no. (%)** | | | | |
| Death from any cause | 711 (17.0) | 835 (19.8) | 0.84 (0.76–0.93) | <0.001 |
| Change in KCCQ clinical summary score at 8 months[b] | -2.99±0.36 | -4.63±0.36 | 1.64 (0.63–2.65) | 0.001 |
| New-onset atrial fibrillation[c] | 84 (3.1) | 83 (3.1) | 0.97 (0.72–1.31) | 0.83 |
| Decline in renal function[d] | 94 (2.2) | 108 (2.6) | 0.86 (0.65–1.13) | 0.28 |

[a]Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons; [b] Scores on KCCQ range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference; [c] A total of 2,670 patients in the sacubitril-valsartan group and 2,638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study; [d] A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate from the value.

CI = confidence interval; CV = cardiovascular; HF = heart failure; HFH = heart failure hospitalization; KCCQ = Kansas City Cardiomyopathy Questionnaire; QOL = quality of life.

**1.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

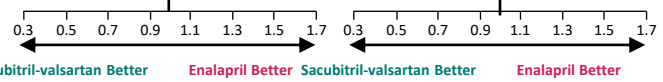
# PARADIGM-HF: SUBGROUP ANALYSES [1]

## Subgroup analyses of the primary end point and CV death favored sacub

- In the VICTORIA study subgroup analysis for time to first HFH, vericiguat treatment showed a significant interaction for 3 subgroup factors:
  - NT-proBNP at baseline by quartiles; HR=0.91; 95% CI, 0.86–0.97; *P*=0.002
  - Age <65 years vs ≥65 years; HR higher for patients aged ≥65 years; *P*=0.036
  - Age <75 years vs ≥75 years; HR comparing vericiguat with placebo was higher for patients aged ≥75 years; *P*=0.045

**Reference**
Merck Sharp & Dohme Corp. Data on file; Bayer AG. Data on file.

| Subgroup | Sacubitril-Valsartan | Enalapril | Primary End Point HR (95% CI) | Primary End Point *P* Value for Interaction | Death from CV Causes HR (95% CI) | Death from CV Causes *P* Value for Interaction |
|---|---|---|---|---|---|---|
| **All patients** | 4,187 | 4,212 | | | | |
| **Age** | | | | 0.47 | | 0.70 |
| **Diabetes** | | | | 0.40 | | 0.05 |
| No | 2,736 | 2,756 | | | | |
| Yes | 1,451 | 1,456 | | | | |
| **Systolic blood pressure** | | | | 0.87 | | 0.62 |
| ≤Median | 2,298 | 2,299 | | | | |
| >Median | 1,889 | 1,913 | | | | |
| **Ejection fraction** | | | | 0.71 | | 0.80 |
| ≤Median | 2,239 | 2,275 | | | | |
| >Median | 1,948 | 1,936 | | | | |
| **Ejection fraction** | | | | 0.36 | | 0.36 |
| ≤35% | 3,715 | 3,722 | | | | |
| >35% | 472 | 489 | | | | |
| Atrial fibrillation | | | | 0.25 | | 1.00 |
| No | 2,670 | 2,638 | | | | |
| Yes | 1,517 | 1,574 | | | | |
| **NT-proBNP** | | | | 0.16 | | 0.33 |
| ≤Median | 2,079 | 2,116 | | | | |
| >Median | 2,103 | 2,087 | | | | |
| **Hypertension** | | | | 0.87 | | 0.14 |
| No | 1,218 | 1,241 | | | | |
| Yes | 2,969 | 2,971 | | | | |
| **Prior use of ACEi** | | | | 0.09 | | 0.06 |
| No | 921 | 946 | | | | |
| Yes | 3,266 | 3,266 | | | | |
| **Prior use of aldosterone antagonist** | | | | 0.10 | | 0.32 |
| No | 1,916 | 1,812 | | | | |
| Yes | 2,271 | 2,400 | | | | |




| Subgroup | Sacubitril-Valsartan | Enalapril | Primary End Point HR (95% CI) | Primary End Point *P* Value for Interaction | Death from CV Causes Hazard Radio (95% CI) | Death from CV Causes *P* Value for Interaction |
|---|---|---|---|---|---|---|
| **Prior HFH** | | | | 0.10 | | 0.19 |
| No | 1580 | 1545 | | | | |
| Yes | 2607 | 2667 | | | | |
| **Time since diagnosis of heart failure** | | | | 0.27 | | 0.21 |
| ≤1 Year | 1275 | 1248 | | | | |
| >1 to 5 years | 1621 | 1611 | | | | |
| >5 year | 1291 | 1353 | | | | |
| **All patients** | 4187 | 4212 | | | | |
| **Age** | | | | 0.47 | | 0.70 |
| <65 years | 2111 | 2168 | | | | |
| ≥65 Years | 2076 | 2044 | | | | |
| **Age** | | | | 0.32 | | 0.62 |
| <75 years | 3403 | 3433 | | | | |
| ≥75 Years | 784 | 779 | | | | |
| **Sex** | | | | 0.63 | | 0.92 |
| Male | 3308 | 3259 | | | | |
| Female | 879 | 953 | | | | |
| **Race** | | | | 0.58 | | 0.88 |
| White | 2763 | 2781 | | | | |
| Black | 213 | 215 | | | | |
| Asian | 759 | 750 | | | | |
| Native American | 84 | 88 | | | | |
| Other | 368 | 378 | | | | |
| **NYHA class** | | | | 0.03 | | 0.76 |
| I or II | | | | | | |
| III or IV | | | | | | |
| **eGFR** | | | | | | |
| <60 mL/min/1.73 m² | | | | | | |
| ≥60 mL/min/1.73 m² | | | | | | |

- In the VICTORIA study subgroup analysis for time to CV death, vericiguat treatment showed a significant interaction for age (<75 years vs ≥75 years; *P*=0.036).
- The HR comparing vericiguat to placebo was higher for patients aged ≥75 years

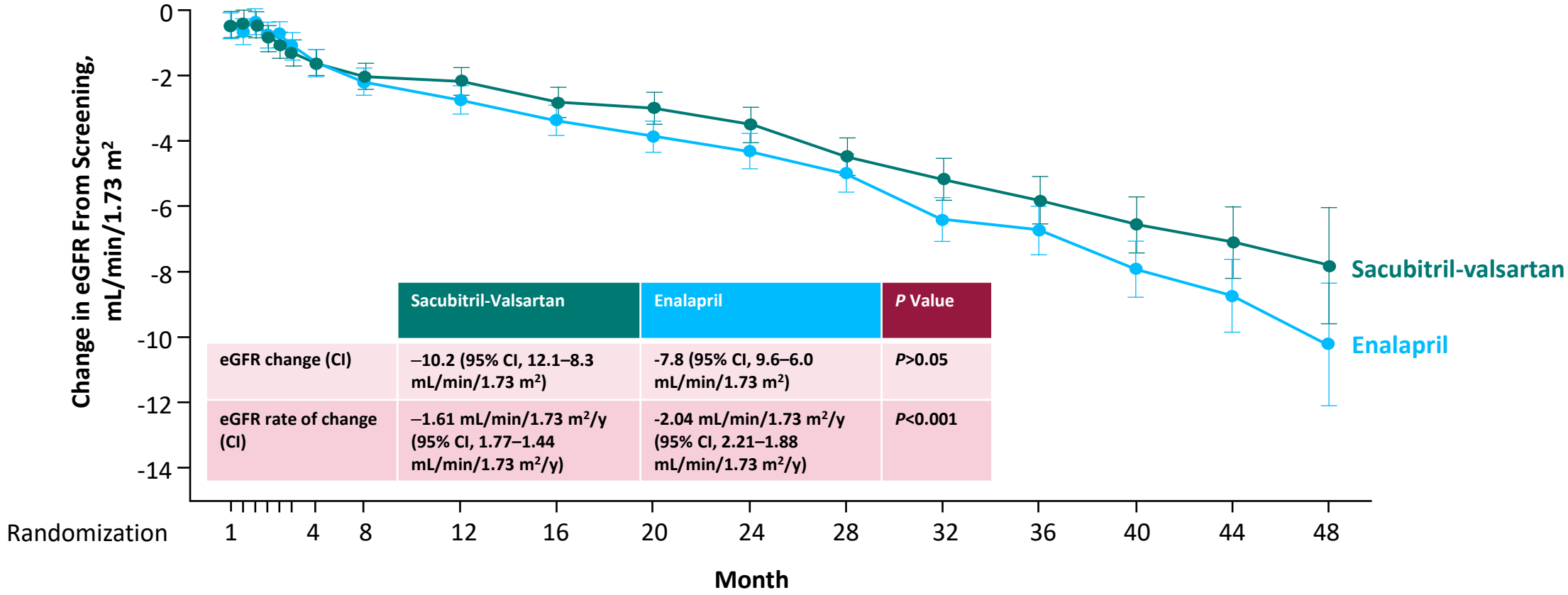
**Reference:**
Merck Sharp & Dohme Corp. Data on file; Bayer AG. Data on file.

ACEi = angiotensin-converting enzyme inhibitor; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HFH = heart failure hospitalization; HR = hazard ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

**1.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

# PARADIGM-HF EXPLORATORY OUTCOME: CHANGE IN eGFR[1]

- **Sacubitril-valsartan resulted in a lower decline in eGFR compared with enalapril, though this difference was not significant**
  - The rate of decrease in the eGFR was significantly less with sacubitril/valsartan compared with enalapril (*P*<0.001)




| | Sacubitril-Valsartan | Enalapril | *P* Value |
|---|---|---|---|
| eGFR change (CI) | –10.2 (95% CI, 12.1–8.3 mL/min/1.73 m²) | -7.8 (95% CI, 9.6–6.0 mL/min/1.73 m²) | *P*>0.05 |
| eGFR rate of change (CI) | –1.61 mL/min/1.73 m²/y (95% CI, 1.77–1.44 mL/min/1.73 m²/y) | -2.04 mL/min/1.73 m²/y (95% CI, 2.21–1.88 mL/min/1.73 m²/y) | *P*<0.001 |

CI = confidence interval; eGFR = estimated glomerular filtration rate.

**1.** Damman K et al. *JACC Heart Fail*. 2018;6:489–498.

# PARADIGM-HF: SAFETY DATA[1]

- Patients in the sacubitril-valsartan group were more likely than those in the enalapril group to have symptomatic hypotension (*P*<0.001)
- In contrast, cough (*P*<0.001), a serum creatinine level of 2.5 mg per deciliter or more (*P=0*.007), and a serum potassium level of more than 6.0 mmol per liter (*P*=0.007) were reported less frequently in the sacubitril-valsartan group than in the enalapril group
- Compared with the value at randomization, the mean SBP at 8 months was 3.2±0.4 mm Hg lower in the sacubitril-valsartan group than it was in the enalapril group (*P*<0.001)

| Adverse Event[a] | Sacubitril-Valsartan (N=4,187) n (%) | Enalapril (N=4,212) n (%) | *P* Value |
|---|---|---|---|
| **Hypotension** | | | |
| **Symptomatic** | **588 (14.0)** | **388 (9.2)** | **<0.001** |
| **Symptomatic with SBP <90 mm Hg** | **112 (2.7)** | **59 (1.4)** | **<0.001** |
| **Elevated serum creatinine** | | | |
| ≥2.5 mg/dL | 139 (3.3) | 188 (4.5) | 0.007 |
| ≥3.0 mg/dL | 63 (1.5) | 83 (2.0) | 0.100 |
| **Elevated serum potassium** | | | |
| >5.5 mmol/L | 674 (16.1) | 727 (17.3) | 0.150 |
| >6.0 mmol/L | 181 (4.3) | 236 (5.6) | 0.007 |
| **Cough** | 474 (11.3) | 601 (14.3) | <0.001 |
| **Angioedema[b]** | | | |
| No treatment or use of antihistamines only | 10 (0.2) | 5 (0.1) | 0.190 |
| Use of catecholamines or glucocorticoids without hospitalization | 6 (0.1) | 4 (0.1) | 0.520 |
| Hospitalization without airway compromise | 3 (0.1) | 1 (<0.1) | 0.310 |
| Airway compromise | 0 | 0 | - |

[a]Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the sacubitril-valsartan group and 29 (0.7%) in the enalapril group (*P*=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (*P=0*.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (*P*=0.56).
[b]Angioedema was adjudicated in a blinded fashion by an expert committee.
SBP = systolic blood pressure.

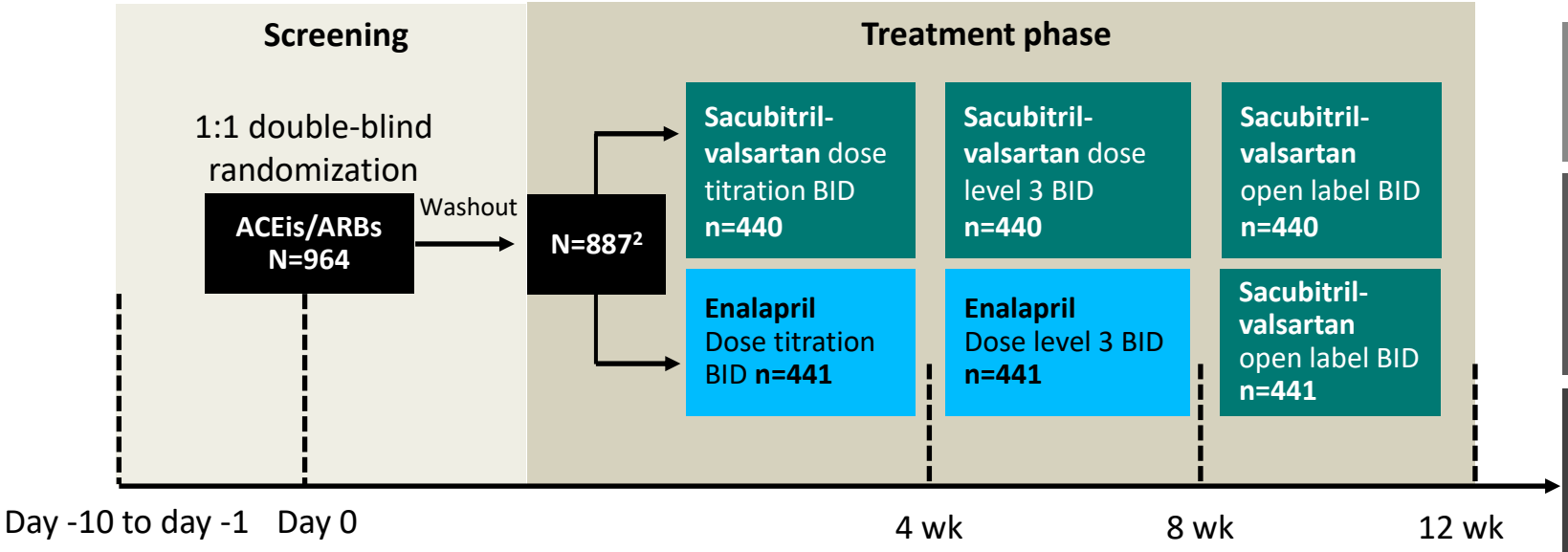
**1.** McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004.

# PIONEER-HF

**A Phase 3 Clinical Trial in 887 Patients With Acute Decompensated HFrEF**

# PIONEER-HF: STUDY DESIGN AND KEY STUDY OUTCOMES

**Study to assess the effect of in-hospital initiation of sacubitril-valsartan vs enalapril on time-averaged proportional change in NT-proBNP in patients who have been stabilized following hospitalization for acute decompensated HF and LVEF ≤40%.[1,2]**




**The study was powered to detect an 18 percentage point–greater time-averaged proportional reduction in the NT-proBNP concentration from the baseline value to the geometric mean of values obtained at weeks 4 and 8.[1]**

## Primary Outcome[2]

Time-averaged proportional change in NT-proBNP from baseline

## Selected Secondary Outcomes[2]

- Change in NT-proBNP at week 8
- Natriuretic peptide system activation (urinary cGMP)
- Cardiac fibrosis/remodeling (sST2)
- Tissue perfusion/injury (hsTnT)

## Selected Exploratory Outcomes[2]

- Change in NT-proBNP at week 1 and 2
- Time to first occurrence of composite of death, hospitalization for worsening HF, left ventricular assist device implantation, listed for cardiac transplantation, unplanned ED or office visit requiring intravenous diuretics, increase in diuretic dose >50%
- Hospitalization or unplanned ED or office visit for HF

ACEis = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BID = twice daily; cGMP = cyclic guanosine monophosphate; ED = emergency department; HF = heart failure; hsTnT = high-sensitivity troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; sST2 = soluble suppression of tumorigenesis-2.

**1.** Velazquez EJ et al. *N Engl J Med*. 2019;380:539–548. **2.** Velazquez EJ et al. *Am Heart J*. 2018;198:145–151.

# PIONEER-HF: BASELINE CHARACTERISTICS AND ELIGIBILITY CRITERIA

## Selected Inclusion Criteria[1]

- Age >18 years
- Currently hospitalized for a primary diagnosis of HF
- Randomized no earlier than 24 h and up to 10 d after initial presentation while still hospitalized
- Stable as defined by an SBP >100 mm Hg for the preceding 6 h in the absence of symptomatic hypotension, no increase in IV diuretics or use of IV vasodilators within the last 6 h, and no IV inotropes for 24 h prior to randomization
- LVEF <40% within the past 6 mo by echocardiography, MUGA, CT scanning, MRI, or ventricular angiography provided no subsequent study documented an EF >40%
- NT-proBNP >1,600 pg/mL or BNP ≥400 pg/mL during the current hospitalization

## Selected Exclusion Criteria[1]

- History of angioedema related to previous ACEi or ARB therapy
- Requirement of treatment with both ACEi and ARB eGFR <30 mL/min/1.73 $m^2$ as measured by the simplified MDRD formula
- History of ACS, stroke, TIA, coronary or carotid revascularization, or major cardiovascular surgery within the past month

## Selected Baseline Characteristics in PIONEER-HF[2,a]

| Variable | Sacubitril–Valsartan (N=440) | Enalapril (N=441) |
|---|---|---|
| **Age – y** | | |
| Median | 61 | 63 |
| Interquartile range | 51–71 | 54–72 |
| **Female – no. (%)** | 113 (25.7) | 133 (30.2) |
| **Race – no. (%)[b]** | | |
| Black | 158 (35.9) | 158 (35.8) |
| White | 261 (59.3) | 254 (57.6) |
| **Body mass index[c]** | | |
| Median | 30.5 | 30.0 |
| Interquartile range | 25.9–37.1 | 25.8–36.3 |
| **Previous HF – no. (%)** | 298 (67.7) | 278 (63.0) |
| **Previous use of medication – no. (%)** | | |
| ACEi or ARB | 208 (47.3) | 214 (48.5) |
| β-blocker | 262 (59.5) | 263 (59.6) |
| MRA | 48 (10.9) | 40 (9.1) |
| Loop diuretic | 262 (59.5) | 240 (54.4) |
| Hydralazine | 30 (6.8) | 33 (7.5) |
| Nitrate | 43 (9.8) | 40 (9.1) |
| Digoxin | 41 (9.3) | 35 (7.9) |
| **NYHA class – no. (%)** | | |
| I | 4 (0.9) | 5 (1.1) |
| II | 100 (22.7) | 122 (27.7) |
| III | 283 (64.3) | 269 (61.0) |
| IV | 39 (8.9) | 36 (8.2) |
| Not assessed | 14 (3.2) | 9 (2.0) |

| Variable | Sacubitril–Valsartan (N=440) | Enalapril (N=441) |
|---|---|---|
| **Pulse – beats per min[§]** | | |
| Median | 81 | 80 |
| Interquartile range | 72–92 | 72–91 |
| **LVEF – %[e]** | | |
| Median | 24 | 25 |
| Interquartile range | 18–30 | 20–30 |
| **NT-proBNP at screening – pg/mL[e]** | | |
| Median | 4,821 | 4,710 |
| Interquartile range | 3,109–8,767 | 2,966–8,280 |
| **NT-proBNP at randomization – pg/mL[d]** | | |
| Median | 2,883 | 2,536 |
| Interquartile range | 1,610–5403 | 1,363–4,917 |
| **Serum creatinine – mg/dL[d]** | | |
| Median | 1.28 | 1.27 |
| Interquartile range | 1.07–1.51 | 1.05–1.50 |
| **eGFR – mg/min/1.73 $m^2$ [d]** | | |
| Median | 58.4 | 58.9 |
| Interquartile range | 47.5–71.5 | 47.4–70.9 |
| **Serum potassium – mmol/L[d]** | | |
| Median | 4.20 | 4.25 |
| Interquartile range | 4.00–4.50 | 3.90–4.60 |
| **SBP – mm HG[d]** | | |
| Median | 118 | 118 |
| Interquartile range | 110–133 | 109–132 |

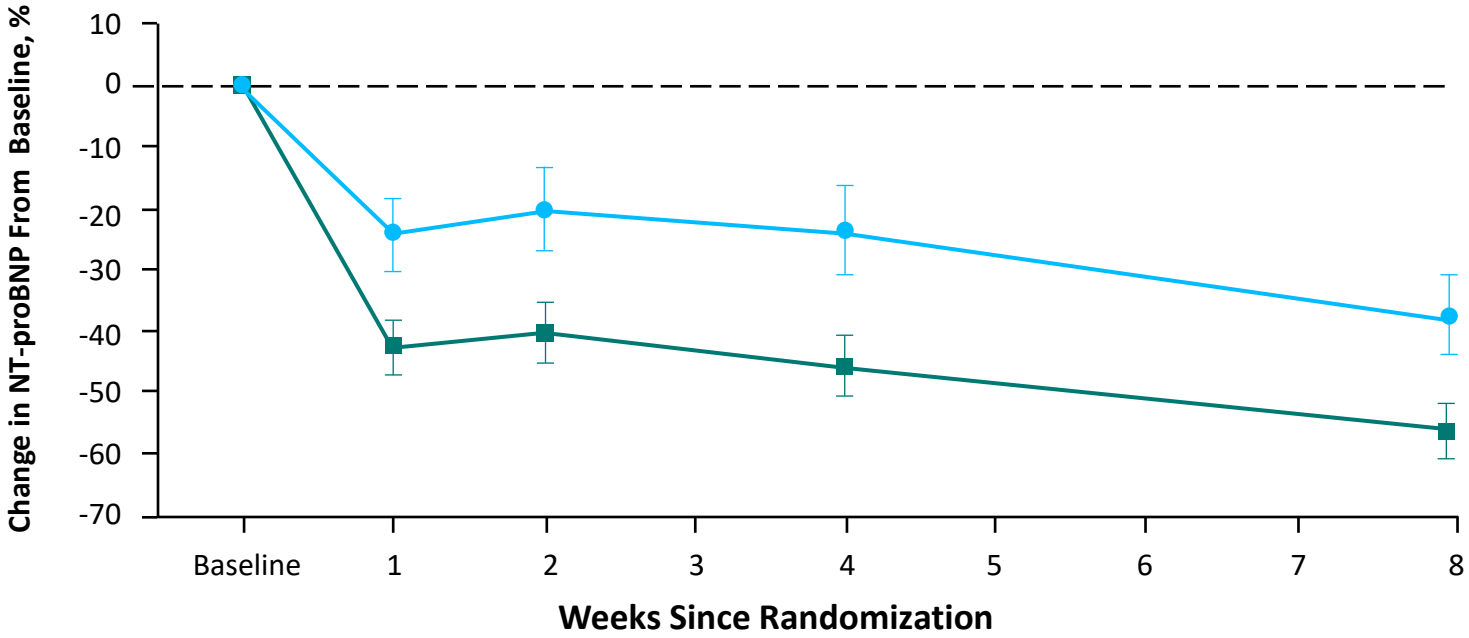
[a]There were no significant differences between the two groups with respect to baseline characteristics, with the exception of the NT-proBNP concentration at randomization ($P$=0.04); [b]Information on race was reported by the patient; [c]The body-mass index is the weight in kilograms divided by the square of the height in meters; [d]The value was obtained at the central laboratory at randomization; [e]The value was obtained at the site laboratory at screening.

ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; BNP = B-type natriuretic peptide; CT = computed tomography; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; IV = intravenous; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; MRA = mineralocorticoid receptor antagonist; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; TIA = transient ischemic attack.

**1.** Velazquez EJ et al. *Am Heart J*. 2018;198:145–151. **2.** Velazquez EJ et al. *N Engl J Med*. 2019;380:539–548.

# PIONEER-HF: PRIMARY OUTCOME—NT-proBNP LEVELS[1]

**The time-averaged reduction in NT-proBNP was significantly greater in the sacubitril-valsartan group than in the enalapril group (*P*<0.001).**




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Enalapril | 394 | 359 | 351 | 350 | 348 |
| Sacubitril-valsartan | 397 | 355 | 363 | 365 | 349 |

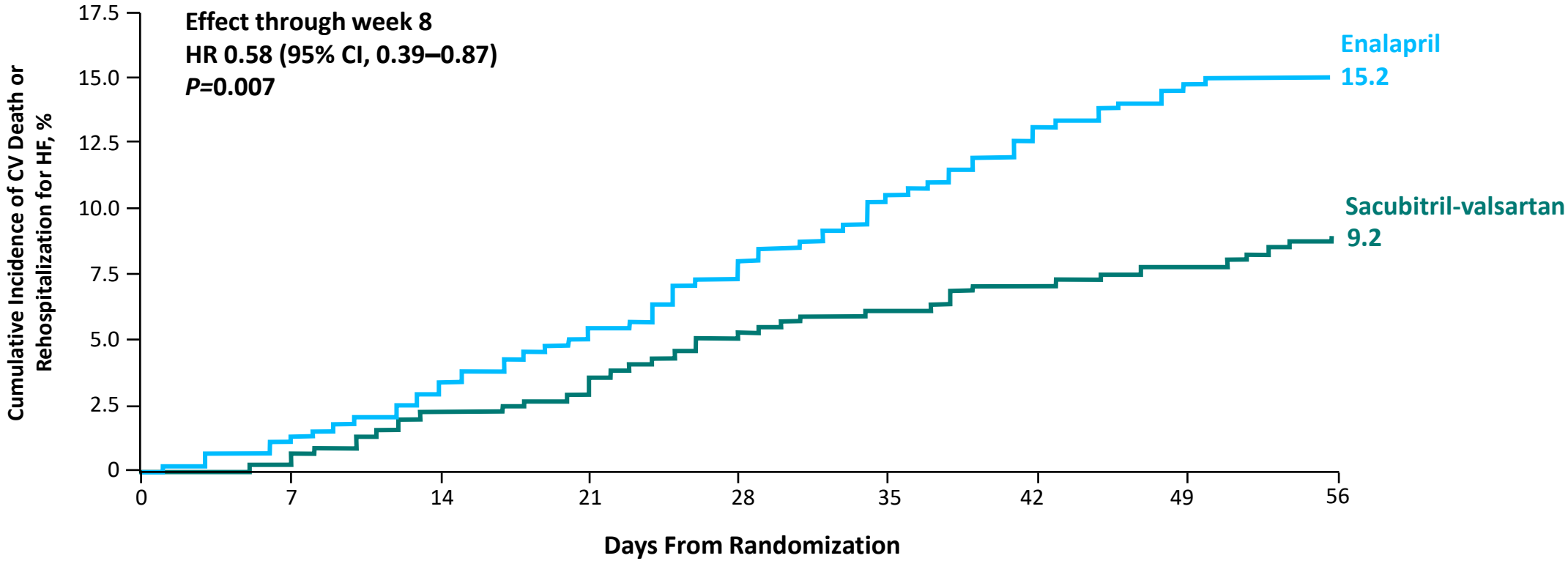
- **Percent change with sacubitril-valsartan vs enalapril was −46.7% vs −25.3%**
- **Ratio of change with sacubitril-valsartan vs enalapril, 0.71; 95% CI, 0.63–0.81; *P*<0.001)**

CI = confidence interval; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

**1.** Velazquez EJ et al. *N Engl J Med*. 2019;380:539–548.

# PIONEER-HF: EXPLORATORY OUTCOME—COMPOSITE OF CV DEATH AND REHOSPITALIZATION FOR HF[1]

**Treatment with sacubitril-valsartan significantly reduced the risk of the composite of CV death and rehospitalization for HF compared with the enalapril group through 8 weeks of follow-up.**

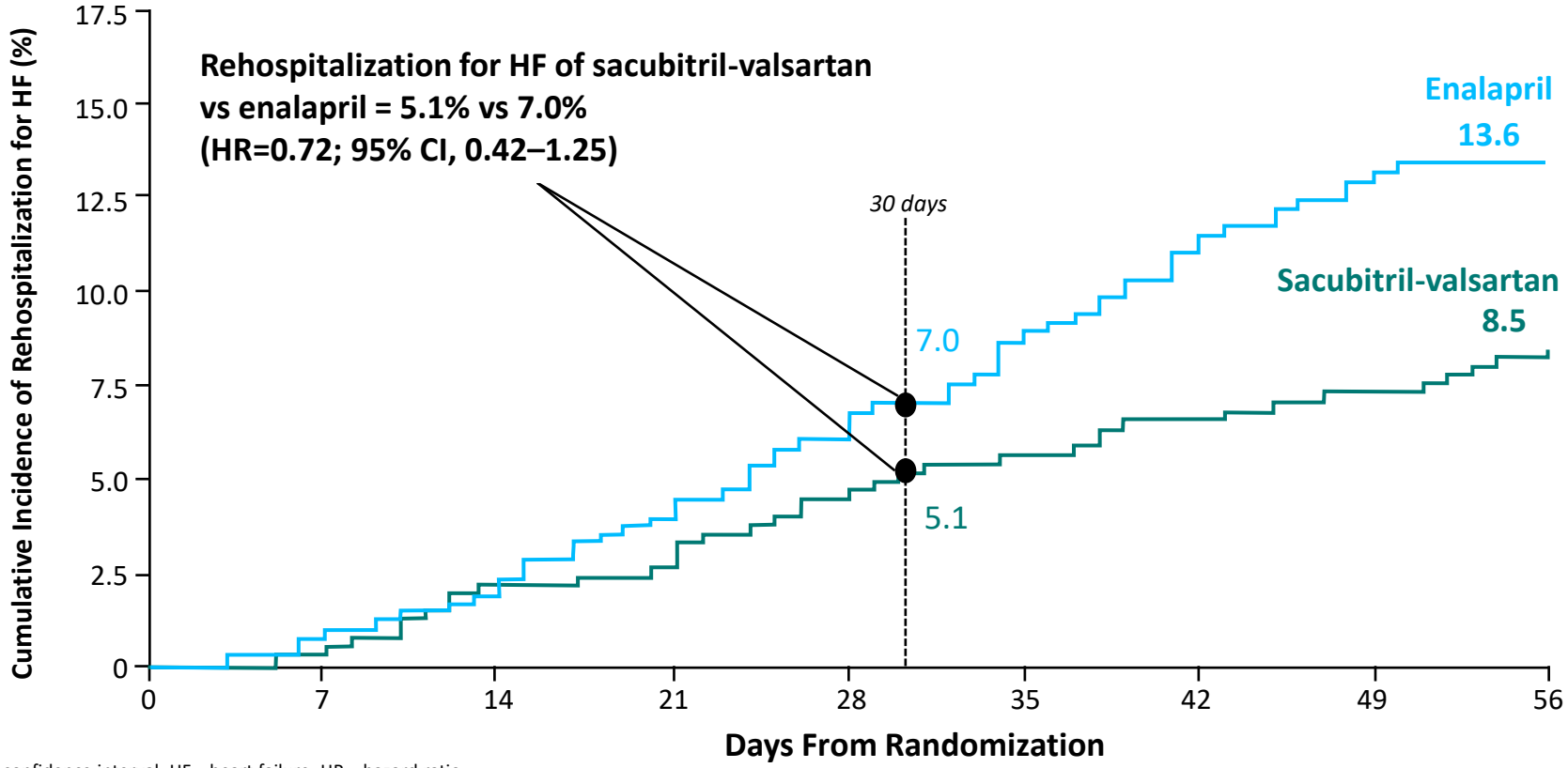



CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.

**1.** Morrow DA et al. *Circulation*. 2019;139:2285–2288.

# PIONEER-HF: REHOSPITALIZATION FOR HF AND EXPLORATORY OUTCOME[1]

- **At 30 days, the rates of rehospitalization for HF were lower for the sacubitril-valsartan group compared with the enalapril group, with this effect still present at week 8**
  - At week 8, the cumulative incidence of cardiovascular death or HF rehospitalization was significantly lower for patients on sacubitril-valsartan vs enalapril (HR=0.58; 95% CI, 0.39–0.87; *P*=0.007)



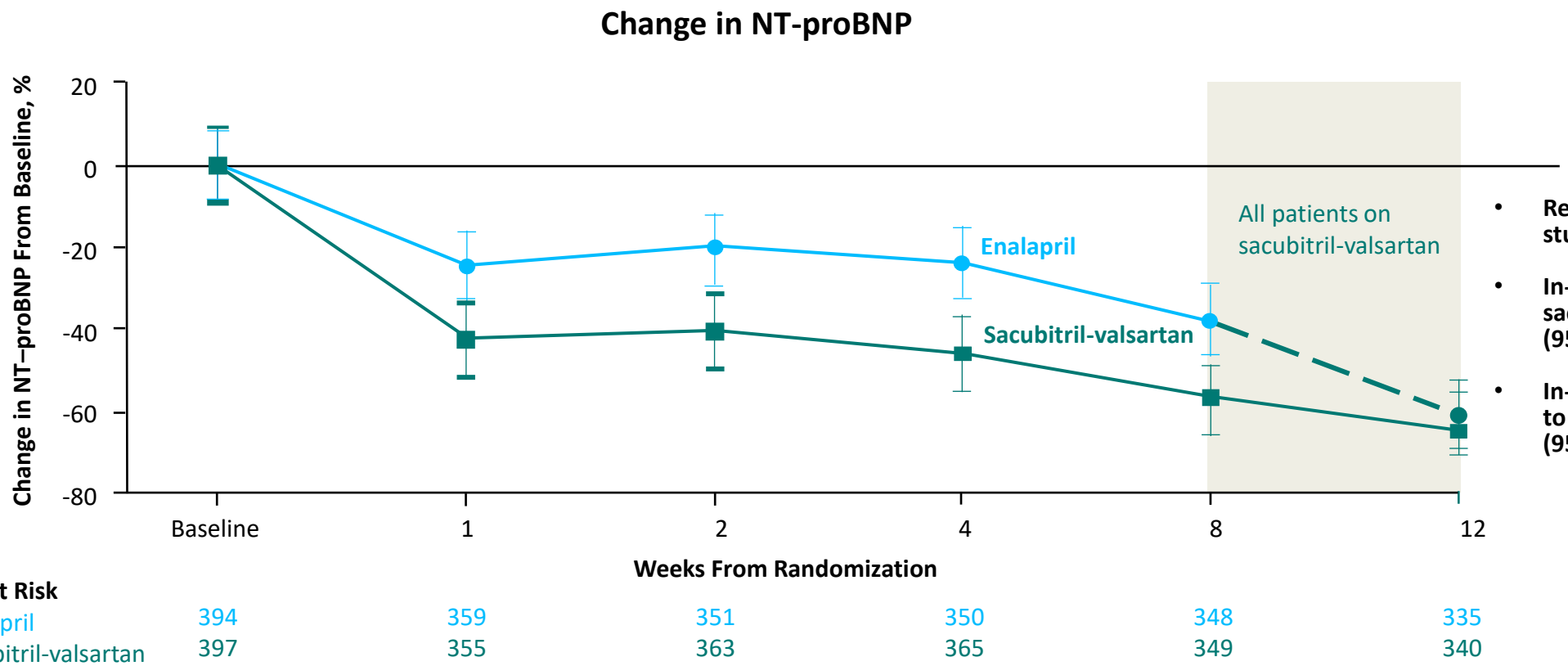

**Rehospitalization for HF through Week 8 = 13.6% vs 8.5% (HR=0.61; 95% CI, 0.40–0.93; *P*=0.021)**

CI = confidence interval; HF = heart failure; HR = hazard ratio.

**1.** Morrow DA et al. *Circulation*. 2019;139:2285–2288.

# PIONEER-HF OPEN LABEL EXTENSION: NT-proBNP LEVELS[1]

**Switching patients from enalapril to Entresto at 8 weeks after randomization led to a further 37% reduction in NT-proBNP in patients with heart failure with reduced ejection fraction and a recent heart failure hospitalization.**




- **Reduction during open-label study, weeks 8–12**
- **In-hospital enalapril to sacubitril-valsartan: -37.4% (95% CI, –28.1 to –45.6)**
- **In-hospital sacubitril-valsartan to sacubitril-valsartan: -17.2% (95% CI, –3.2 to –29.1; *P*<0.001)**

CI = confidence interval; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

**1.** DeVore AD et al. *JAMA Cardiol*. 2020;5:202–207.

# PIONEER-HF: SAFETY AND SECONDARY/EXPLORATORY OUTCOMES[1]

**The rates of worsening renal function, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril-valsartan group and the enalapril group.**

| Outcome[a] | Sacubitril-Valsartan (N=440) | Enalapril (N=441) | Sacubitril-Valsartan vs Enalapril |
|---|---|---|---|
| **Key safety outcomes, no. (%)** | | | **Relative risk (95% CI)** |
| Worsening renal function[b] | 60 (13.6) | 65 (14.7) | 0.93 (0.67–1.28) |
| **Hyperkalemia** | **51 (11.6)** | **41 (9.3)** | **1.25 (0.84–1.84)** |
| **Symptomatic hypotension** | **66 (15.0)** | **56 (12.7)** | **1.18 (0.85–1.64)** |
| Angioedema | 1 (0.2) | 6 (1.4) | 0.17 (0.02–1.38) |
| **Secondary biomarker outcomes, % (95% CI)[c]** | | | **Ratio of change (95% CI)** |
| Change in high-sensitivity troponin T concentration | –36.6 (–40.8 to –32.0) | –25.2 (–30.2 to –19.9) | 0.85 (0.77–0.94) |
| Change in B-type natriuretic peptide concentration | –28.7 (–35.5 to –21.3) | –33.1 (–39.5 to –25.9) | 1.07 (0.92–1.23) |
| Change in ratio of B-type natriuretic peptide to NT-proBNP | 35.2 (28.8– 42.0) | –8.3 (–3.6 to –12.7) | 1.48 (1.38–1.58) |
| **Exploratory clinical outcomes, no. (%)** | | | **Hazard ratio (95% CI)[d]** |
| Composite of clinical events | 249 (56.6) | 264 (59.9) | 0.93 (0.78–1.10) |
| Death | 10 (2.3) | 15 (3.4) | 0.66 (0.30–1.48) |
| Rehospitalization for heart failure | 35 (8.0) | 61 (13.8) | 0.56 (0.37–0.84) |
| Implantation of left ventricular assist device | 1 (0.2) | 1 (0.2) | 0.99 (0.06–15.97) |
| Inclusion of list for heart transplantation | 0 | 0 | NA |
| Unplanned outpatient visit leading to use of intravenous diuretics | 2 (0.5) | 2 (0.5) | 1.00 (0.14–7.07) |
| Use of additional drug for heart failure | 78 (17.7) | 84 (19.0) | 0.92 (0.67–1.25) |
| Increase in dose of diuretics of >50% | 218 (49.5) | 222 (50.3) | 0.98 (0.81–1.18) |
| Composite of serious clinical events[e] | 41 (9.3) | 74 (16.8) | 0.54 (0.37–0.79) |

[a]NA denotes not available; [b]Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more (≥44 µmol per liter) and a decrease in the estimated glomerular filtration rate of 25% or more; [c]Shown are data on the time-averaged proportional change, from the baseline value to the geometric mean of values obtained at weeks 4 and 8; [d]Hazard ratios and associated 95% CIs were calculated with a Cox proportional-hazards model. CIs have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible; [e]The outcome of a composite of serious clinical events was added to the list of exploratory clinical outcomes in May 2018, before the database was locked and unblinding occurred. This end point included death, rehospitalization for heart failure, implantation of a left ventricular device, and inclusion on the list of patients eligible for heart transplantation.

CI = confidence interval; NA = not available; NT-proBNP N-terminal pro-brain natriuretic peptide.

**1.** Velazquez EJ et al. *N Engl J Med*. 2019;380:539–548.

# Summary

- Despite use of guideline-directed medical therapy, patients are at increased risk of poor prognosis after a worsening HF event1
- Use of sacubitril/valsartan has demonstrated clinically meaningful improvements in patients with HFrEF, but there is still a high residual risk of CV death or HFH2

**PARADIGM HF:**

- **21.8% of patients on sacubitril/valsartan died from CV causes or had a first hospitalisation for worsening HF after a median follow-up of 27 months in PARADIGM-HF2**
- **Hypotension, hyperkalaemia and renal insufficiency were the most frequently cited reasons for underdosing, underuse and discontinuation of RAASis3**
- **A significantly greater number of patients experienced hypotension when treated with sacubitril/valsartan compared with enalapril in PARADIGM-HF4**
- **Within the patient group treated with sacubitril/valsartan, 54.1% (393/726) of hypotension events led to dose adjustment or temporary discontinuation, and 2.2% (16/726) of events led to permanent discontinuation5**
- **Rates of symptomatic hypotension and syncope were similar between vericiguat and placebo in VICTORIA1**
- **PARADIGM-HF contained a pre-selected patient population. The run-in phase enabled patients intolerant of sacubitril/valsartan to be excluded from the study, potentially leading to an overestimation of the effect size and underestimation of risk by screening for patients who were able to tolerate the side-effect profile4,7**

**PIONEER-HF trial**

- Although  not powered for clinical outcomes, showed that among patients who were hospitalised for acute decompensated heart failure, the initiation of sacubitril/valsartan therapy resulted in a significantly greater reduction in NT-proBNP concentration than enalapril therapy. Of note, the patient population in PIONEER-HF was similar to that of VICTORIA; the median NT-proBNP at baseline in VICTORIA compared with PIONEER-HF was 2816 pg/ml and 2710 pg/ml, respectively4,5