Success of ARNI Continues in 2019: An Update

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I disclose the following relationships with industry that are relevant to my talk:

- **Grants:** Roche Diagnostics, Prevencio, Novartis, Abbott, Cleveland Heart Labs
- **Consulting:** Roche Diagnostics, Novartis, Janssen
- **Endpoint/DSMB committees:** Abbott, AbbVie, Amgen, Bayer, Boehringer-Ingelheim, Janssen, Pfizer, Takeda
Overactivation of the RAAS and SNS is Detrimental in HFrEF and Underpins the Basis of Therapy

Natriuretic peptide system
NPRs ↔ NPs
Vasodilation
↓ Blood pressure
↓ Sympathetic tone
↑ Natriuresis/diuresis
↓ is
↓ Vasopressin
↓ Aldosterone
↓ Fibrosis
↓ Hypertrophy

RAAS
Ang II → AT₁ R
Vasoconstrictio
n ↑
RAAS activity ↑
Vasopressin ↑
Heart rate ↑
Contractility

β-blockers
Epinephrine
Norepinephrine
α₁, β₁, β₂ receptors

Natriuresis/diuresis
↓
Blood pressure
↓
Sympathetic tone
↓
Aldosterone
↓
Fibrosis
↓
Hypertrophy
↓

Natriuretic peptide systems oppose the RAAS

- **ANP/CNP**
- **BNP**

**Natriuretic peptide signaling cascades**
- Gene expression; ↑ protein synthesis; ↑ cell proliferation
- Inactive peptides
- Internalization
- Receptor recycling

**Vasodilation**
- ↑ Cardiac fibrosis/hypertrophy
- ↑ Natriuresis/diuresis

**Vasoconstriction**
- ↑ Cardiac fibrosis/hypertrophy
- ↑ Sodium/water retention

**Inactive NP fragments**
- Neprilysin
- NPR-A
- NPR-B
- NPR-C

**AT1 receptor**
- ANP
- BNP
- CNP
- ANP/CNP
- Ang II

**GTP**
- cGMP
NEP and vasoactive peptides

**Relative affinity for NEP**

- ANP / CNP
  - Ang II
  - Ang I
  - Adrenomedullin
  - Substance P
  - Bradykinin
  - Endothelin
  - BNP

**NEP and vasoactive peptides**

- Inactive fragments or metabolites

**Implications for NEP inhibition**

- NEP substrates can have opposing biological actions
  - Overall effect is dependent upon the **net effect** on NEP metabolism of multiple substrates
  - Benefits in enhancing NP system may be offset by increased Ang II
  - **Needs to be complemented by simultaneous RAAS suppression**
Sacubitril/valsartan: "blocking the bad and and increasing the good"

Enhancing the natriuretic peptide system

Supressing the RAAS

Inactive NP fragments

Sacubitril

ANP/CNP/BNP

NPR-A

GTP

NPR-B

GTP

Sac/val

NPR-C

BNP

AT1 receptor

Vasoconstriction

↑ Cardiac fibrosis/hypertrophy

↑ Sodium/water retention

Vasodilation

↓ Cardiac fibrosis/hypertrophy

↑ Natriuresis/diuresis

Gene expression; ↑ protein synthesis; ↑ cell proliferation

Receptor recycling

Inactive peptides

Internalization

ANP/CNP/BNP

GTP

cGMP

Nepriysin

ANP

BNP

CNP
The PARADIGM-HF Trial

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>0-180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>180-360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>360-540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>540-720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>720-900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>900-1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1080-1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>


Kaplan-Meier Estimate of Cumulative Rates (%)

- Enalapril (n=4212): 1117 (26.5%)
- LCZ696 (n=4187): 914 (21.8%)

HR = 0.80 (0.73-0.87)
P = 0.0000004
Number needed to treat = 21

15% at 1 yr
Effect of ARNI on mode of death

Effect of ARNI compared to other RAS inhibitors

Pharmacological Treatment for Stage C HFrEF

<p>| Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI |
|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>ARNI: B-R</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
</tr>
</tbody>
</table>

COR = Class of Recommendations
LOE = Level of Evidence
So, what’s new in 2019?

• Improved understanding of mechanism of action in **chronic** heart failure with reduced ejection fraction

• Expanded role in **acute** heart failure with reduced ejection fraction

• Clarity on the role of ARNI in chronic heart failure with preserved ejection fraction
So, what’s new in 2019?

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BNP and NT-proBNP in PARADIGM-HF

- Concentrations of **NT-proBNP generally decrease** after initiation of sacubitril/valsartan.
- Concentrations of **BNP generally increase (by around 20-25%)** after initiation of sacubitril/valsartan.
- This elevation does not “wear off” over time, as all NP concentrations (including NT-proBNP) were falling by 1 year.

Myhre, et al, JACC 2019
Effect of Nepriylisin Inhibition on Various Natriuretic Peptide Assays

Nasrin E. Brukhim, MD, PhD; Ciro P. McCarthy, MB BCh, BAO; Shinya Shouno, MD; Hans K. Gaggin, MD; MPH;1,2
Irene Mukai, BA; Jackie Sayson, MA; Fred S. Apple, PhD; John C. Burnett, Jr, MD;2
Seethalakshmi Iyer, MS PA-C; James L. Januzzi, Jr, MD1,3

ABSTRACT

BACKGROUND: With sacubitril/valsartan treatment, 31-hydroxy natriuretic peptide (31-NP) concentrations increase, it remains unclear whether change in BMP concentrations is similar across all assays for its measurement. Effects of sacubitril/valsartan on atrial natriuretic peptide (ANP) concentrations in patients are unknown. Lastly, the impact of nepriylisin inhibition on pro-regional pro-ANP (npro-ANP), N-terminal pro-BNP (NT-proBNP), proBNP1-65, or C-type natriuretic peptide (CNP) is not well understood.

OBJECTIVES: This study sought to examine the effects of sacubitril/valsartan on results from different natriuretic peptide assays.

METHODS: Twenty-three consecutive stable patients with heart failure and reduced ejection fraction were initiated and titrated on sacubitril/valsartan. Change in ANP, NproANP, BMP (using 3 assays), NT-proBNP (3 assays), proBNP1-65, and CNP were measured over 3 visits.

RESULTS: Average time to 3 follow-up visits was 22.4 , and 84 days. ANP rapidly and substantially increased with initiation and titration of sacubitril/valsartan, more than doubling by the first follow-up visit (4.105%). Magnitude of ANP increase was greatest in those with concentrations above the median at baseline (1.38%) compared with those with lower baseline concentrations (-44%). ANP increases were sustained. Treatment with sacubitril/valsartan led to inconsistent changes in BMP, which varied across methods assessed. Concentrations of NproANP, NT-proBNP, and proBNP1-65 variably declined after treatment, whereas CNP concentrations showed no consistent change.

CONCLUSIONS: Initiation and titration of sacubitril/valsartan led to variable changes in concentrations of multiple natriuretic peptides. These results provide important insights to the effects of sacubitril/valsartan treatment on individual patient results, and further suggest the benefit of nepriylisin inhibition may be partially mediated by increased ANP concentrations. J Am Coll Cardiol 2019;73(11):1273-1284

Heterogeneity of effect on NP assays

Maximal % change after treatment

Maximal rise by 3rd visit

Maximal drop by 2nd visit

Does ANP mediate effects of sacubitril/valsartan?

- ANP concentrations increased in every patient
- Average increase >100% rise
- Patients with higher pre-treatment ANP had a post-treatment increase of >300%

Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure (PROVE-HF; NCT02887183)

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\textsuperscript{1}Massachusetts General Hospital, \textsuperscript{2}Baim Institute for Clinical Research, Boston, MA, USA; \textsuperscript{3}Novartis Pharmaceuticals, East Hanover, NJ, USA; \textsuperscript{4}University of Mississippi Medical Center, Jackson, MS, USA; \textsuperscript{5}Duke University Medical Center and Duke Clinical Research Institute, Durham, NC, USA; \textsuperscript{6}University of California, San Diego School of Medicine, San Diego, CA, USA; \textsuperscript{7}Detroit Medical Center, Detroit, MI, USA; \textsuperscript{8}Brigham and Women’s Hospital, Boston, MA, USA
Methods

- Adult patients with symptomatic HFrEF (LVEF ≤40%) eligible for on-label treatment with S/V were enrolled
- Following discontinuation of ACEI/ARB, S/V was initiated and titrated
- Blood samples (x) were obtained at each study visit for NT-proBNP measurement
- An echocardiogram was performed at baseline, 6- and 12-months, and interpreted by a core lab in a clinically and temporally blinded fashion

### Key Inclusion Criteria

- Aged ≥18 years
- Patients with HFrEF who are candidates for on-label sacubitril/valsartan treatment per the standard of care
- NYHA functional class II, III, or IV
- LVEF ≤40% within the preceding 6 months according to any local measurement, and no subsequent documentation of EF >40%
- Stable dose of loop diuretic for the 2 weeks preceding study start

### Key Exclusion Criteria

- History of hypersensitivity/allergy or suspected contraindication to ACEI, ARB, or ARNI
- Any angioedema history
- Concomitant use of ACEI therapy, nesiritide, aliskiren, or drugs that may affect absorption of the study medication
- Current or previous treatment with sacubitril/valsartan
- Inadequate washout of other investigational drugs before study initiation
- Enrollment in another clinical trial within 30 days of screening
- Potassium >5.2 mEq/L at screening
- History of malignancy within 1 year
- Pregnancy, lactation, or use of any method of contraception that is not highly effective
- Implantation of CRT/D within 6 months
- Prior or planned heart transplant or LVAD

Rapid and significant reduction of NT-proBNP was observed, with majority of reduction within the first 2 weeks.
Primary endpoint

- From baseline to 12 months, significant correlations were observed between the change in NT-proBNP concentration and cardiac remodeling parameters.

- Parallel latent growth curve analyses demonstrated strong association between early NT-proBNP change and subsequent reverse cardiac remodeling.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pearson r (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (pg/mL) / LVEF (%)</td>
<td>-0.381 (-0.448, -0.310)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) / LVEDVi (mL/m²)</td>
<td>0.320 (0.246, 0.391)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) / LVESVi (mL/m²)</td>
<td>0.405 (0.335, 0.470)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) / LAVi (mL/m²)</td>
<td>0.263 (0.186, 0.338)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) / E/E’</td>
<td>0.269 (0.182, 0.353)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

IQR, interquartile range; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; mL, milliliter; LAVi, left atrial volume index; E/E’, ratio of early diastolic filling velocity and early diastolic mitral annular velocity.
Reverse cardiac remodeling (1)

Baseline to 12 months: all P < .001

BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index
Reverse cardiac remodeling (2)

Baseline to 12 months: all P <.001

LAVi fell from 37.76 to 30.19 mL/m² (mean: 7.57 mL/m²; P <.001)

E/e’ ratio fell from 11.70 to 10.47 (mean: 1.23; P <.001)

LVMi fell from 124.77 to 107.82 g/m² (mean: -16.00 g/m²; P <.001)

BL, baseline; mL, milliliter; LA, left atrial; LAVi, left atrial volume index; E/e’, ratio of early diastolic filling velocity and early diastolic mitral annular velocity; LVMi, left ventricular mass index.
Subgroups of interest

- Reverse cardiac remodeling was comparable in each subgroup of interest

All \( P < 0.001 \) except where noted

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LS Mean change, BL to 12 months (95% CI)</th>
<th>Parameter</th>
<th>LS Mean change, BL to 12 months (95% CI)</th>
<th>Parameter</th>
<th>LS Mean change, BL to 12 months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>+12.8 (+11.05, +14.5)</td>
<td>LVEF (%)</td>
<td>+9.4 (+8.6, +10.3)</td>
<td>LVEF (%)</td>
<td>+9.4 (+8.4, +10.3)</td>
</tr>
<tr>
<td>LVEDVi (mL/m²)</td>
<td>-13.81 (-15.78, -11.83)</td>
<td>LVEDVi (mL/m²)</td>
<td>-11.32 (-12.24, -10.40)</td>
<td>LVEDVi (mL/m²)</td>
<td>-10.99 (-12.21, -9.77)</td>
</tr>
<tr>
<td>LVESVi (mL/m²)</td>
<td>-17.88 (-20.07, -15.68)</td>
<td>LVESVi (mL/m²)</td>
<td>-14.15 (-15.15, -13.15)</td>
<td>LVESVi (mL/m²)</td>
<td>-14.32 (-15.67, -12.97)</td>
</tr>
<tr>
<td>LAVi (mL/m²)</td>
<td>-8.44 (-9.73, -7.15)</td>
<td>LAVi (mL/m²)</td>
<td>-7.06 (-7.54, -6.58)</td>
<td>LAVi (mL/m²)</td>
<td>-7.23 (-7.97, -6.50)</td>
</tr>
<tr>
<td>E/e'</td>
<td>-2.60 (-3.83, -1.37)</td>
<td>E/e'</td>
<td>-0.93 (-1.43, -0.43)</td>
<td>E/e'</td>
<td>-0.46 (-1.32, +0.40); ( P = \text{NS} )</td>
</tr>
</tbody>
</table>

*NT-proBNP < 600 pg/mL if not hospitalized or < 400 pg/mL if hospitalized within the past 12 months; BNP < 150 pg/mL if not hospitalized or < 100 pg/mL if hospitalized for HF within the past 12 months; BL, baseline; LS, least-square; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; mL, milliliter; LAVi, left atrial volume index; E/E', ratio of early diastolic filling velocity and early diastolic mitral annular velocity; NP, natriuretic peptide.
So, what’s new in 2019?

- Improved understanding of mechanism of action in chronic heart failure with reduced ejection fraction
- Expanded role in acute heart failure with reduced ejection fraction
- Clarity on the role of ARNI in chronic heart failure with preserved ejection fraction
PIONEER: ARNI in acute HFrEF

- Patients admitted to the hospital with acute HFrEF, NYHA class II-IV
- At randomization (between 24 hours and 10 days from initial presentation), hospitalized patients were defined as stable by:
  - SBP ≥100 mmHg for 6 hours prior to randomization, and no symptomatic hypotension
  - No increase (intensification) in IV diuretic dose within 6 hours prior to randomization
  - No IV inotropic drugs for 24 hours prior to randomization
  - No IV vasodilators including nitrates within last 6 hours prior to randomization

- **Primary End Point:** Proportional change in NT-proBNP at weeks 4 and 8

- **Exploratory Clinical Outcome:** Incidence of major CV events, including rehospitalization through day 30

### Table 2. Secondary Efficacy and Safety Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacubitril–Valsartan (N = 440)</th>
<th>Enalapril (N = 441)</th>
<th>Sacubitril–Valsartan vs. Enalapril</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory clinical outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of clinical events</td>
<td>249 (56.6)</td>
<td>264 (59.9)</td>
<td>0.93 (0.78 to 1.10)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>10 (2.3)</td>
<td>15 (3.4)</td>
<td>0.66 (0.30 to 1.48)</td>
<td></td>
</tr>
<tr>
<td>Rehospitalization for heart failure</td>
<td>35 (8.0)</td>
<td>61 (13.8)</td>
<td>0.56 (0.37 to 0.84)</td>
<td></td>
</tr>
<tr>
<td>Implantation of left ventricular assist device</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0.99 (0.06 to 15.97)</td>
<td></td>
</tr>
<tr>
<td>Inclusion on list for heart transplantation</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Unplanned outpatient visit leading to use of intravenous diuretics</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>1.00 (0.14 to 7.07)</td>
<td></td>
</tr>
<tr>
<td>Use of additional drug for heart failure</td>
<td>78 (17.7)</td>
<td>84 (19.0)</td>
<td>0.92 (0.67 to 1.25)</td>
<td></td>
</tr>
<tr>
<td>Increase in dose of diuretics of &gt;50%</td>
<td>218 (49.5)</td>
<td>222 (50.3)</td>
<td>0.98 (0.81 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Composite of serious clinical events</td>
<td>41 (9.3)</td>
<td>74 (16.8)</td>
<td>0.54 (0.37 to 0.79)</td>
<td></td>
</tr>
</tbody>
</table>
Impact of ARNI on HF hospitalization

30-Day HF Readmission

- Sacubitril/Valsartan
  - 8.0%
  - n=440

- Enalapril
  - 13.8%
  - n=441

HR: 0.56
(95% CI 0.37-0.84)
P=0.005

44%*

5.8% Absolute Risk Reduction

Practical tips regarding in-hospital initiation

- **Education**: Involve nursing and pharmacy early and often

- **Safety**
  - Discontinue ACEi 36 hours before starting sacubitril/valsartan
  - Initiate after patient is receiving less intensive loop diuretic

- It is critical to ensure patient has a supply of drug prior to discharge and their insurance has been addressed
So, what’s new in 2019?

• Improved understanding of mechanism of action in **chronic** heart failure with reduced ejection fraction

• Expanded role in **acute** heart failure with reduced ejection fraction

• Clarity on the role of ARNI in chronic heart failure with preserved ejection fraction
PARAGON-HF

- Randomized trial of 4796 patients with HFpEF
  - ≥ 50 years of age and LVEF ≥ 45%
  - Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s)
  - Structural heart disease (LAE or LVH by echocardiography)
  - Elevation in natriuretic peptides

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death.

Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

PARAGON-HF primary results
Recurrent event analysis of total HF hospitalizations and CV death*

Valsartan (n = 2389)
1009 events, 14.6 per 100 pt-years

Sacubitril/valsartan (n = 2407)
894 events, 12.8 per 100 pt-years

Rate ratio 0.87 (95% CI 0.75, 1.01)
p = 0.059

*Semiparametric LWYY method.
HF hospitalizations and CV death

**HF hospitalizations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
<th>Rate ratio 0.85 (95% CI 0.72, 1.00)</th>
<th>p = 0.056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>797</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>690</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CV death**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Hazard ratio 0.95 (95% CI 0.79, 1.16)</th>
<th>p = 0.62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>204</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Semiparametric LWYY method*
# Sensitivity and supportive analyses for primary endpoint

Consistent with primary endpoint

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>Estimate (RR or HR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis LWYY (stratified by region) – adjudicated</td>
<td>RR = 0.87 (0.75, 1.01)</td>
<td>0.059</td>
</tr>
<tr>
<td>Primary analysis (LWYY) including adjudicated urgent HF visits in composite</td>
<td>RR = 0.86 (0.75, 0.99)</td>
<td>0.040</td>
</tr>
<tr>
<td>Investigator reported events (LWYY)</td>
<td>RR = 0.84 (0.74, 0.97)</td>
<td>0.014</td>
</tr>
<tr>
<td>Negative binomial method</td>
<td>RR = 0.87 (0.74, 1.01)</td>
<td>0.066</td>
</tr>
<tr>
<td>Primary analysis LWYY (stratified by country)*</td>
<td>RR = 0.86 (0.75, 0.997)</td>
<td>0.045</td>
</tr>
<tr>
<td>Time to first composite event (CV death or HF hospitalization)</td>
<td>HR = 0.92 (0.81, 1.03)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Post-hoc analysis; LWYY, Lin, Wei, Yang, Ying; RR, rate ratio.
## Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan N = 2316</th>
<th>Valsartan N = 2302</th>
<th>Effect size (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA functional classification at 8 months</strong>&lt;br&gt;Change from baseline (%)</td>
<td>Improved 15.0%&lt;br&gt;Unchanged 76.3%&lt;br&gt;Worsened 8.7%</td>
<td>Improved 12.6%&lt;br&gt;Unchanged 77.9%&lt;br&gt;Worsened 9.6%</td>
<td>OR for improvement 1.45 (1.13, 1.86)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>KCCQ clinical summary score at 8 months</strong>&lt;br&gt;Change from baseline (SE)</td>
<td>-1.6 (0.4)</td>
<td>-2.6 (0.4)</td>
<td>LSM of difference = 1.03 (0.00, 2.1)</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>KCCQ responder</strong>&lt;br&gt;(&gt; than 5-point improvement)</td>
<td>33.0%</td>
<td>29.6%</td>
<td>OR = 1.30 (1.04, 1.61)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Worsening Renal Function</strong>&lt;br&gt;Composite of renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline.</td>
<td>1.4%</td>
<td>2.7%</td>
<td>HR = 0.50 (0.33, 0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>All-cause mortality (%)</strong></td>
<td>14.2%</td>
<td>14.6%</td>
<td>HR = 0.97 (0.84, 1.13)</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Pre-specified subgroups for primary endpoint
Evidence for overall heterogeneity

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events /patients</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1903/4796</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 65 years</td>
<td>276/825</td>
<td>0.99 (0.64–1.53)</td>
</tr>
<tr>
<td>65 years or older</td>
<td>1627/3971</td>
<td>0.85 (0.73–0.99)</td>
</tr>
<tr>
<td>Less than 75 years</td>
<td>938/2597</td>
<td>0.82 (0.66–1.02)</td>
</tr>
<tr>
<td>75 years or older</td>
<td>965/2199</td>
<td>0.92 (0.76–1.11)</td>
</tr>
<tr>
<td>Sex*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>980/2317</td>
<td>1.03 (0.85–1.25)</td>
</tr>
<tr>
<td>Female</td>
<td>923/2479</td>
<td>0.73 (0.59–0.90)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1542/3907</td>
<td>0.83 (0.71–0.97)</td>
</tr>
<tr>
<td>Black</td>
<td>89/102</td>
<td>0.69 (0.24–1.99)</td>
</tr>
<tr>
<td>Asian</td>
<td>237/607</td>
<td>1.25 (0.87–1.79)</td>
</tr>
<tr>
<td>Other</td>
<td>35/180</td>
<td>1.03 (0.47–2.28)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>478/559</td>
<td>0.80 (0.57–1.14)</td>
</tr>
<tr>
<td>Latin America</td>
<td>83/370</td>
<td>1.33 (0.75–2.36)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>544/1390</td>
<td>0.69 (0.53–0.89)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>466/1715</td>
<td>0.97 (0.76–1.24)</td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>332/762</td>
<td>1.10 (0.79–1.52)</td>
</tr>
</tbody>
</table>

Multivariate interaction p < 0.05.
Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex

Only interactions for sex and ejection fraction remained nominally significant.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events/patients</th>
<th>Rate ratio (95% CI)</th>
<th>Primary endpoint</th>
<th>Multivariable interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>980/2317</td>
<td>1.03 (0.85–1.25)</td>
<td></td>
<td>P &lt; 0.006</td>
</tr>
<tr>
<td>Female</td>
<td>923/2479</td>
<td>0.73 (0.59–0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at or below median (57%)</td>
<td>1048/2495</td>
<td>0.78 (0.64–0.95)</td>
<td></td>
<td>P = 0.03 (categorical)</td>
</tr>
<tr>
<td>above median (57%)</td>
<td>855/2301</td>
<td>1.00 (0.81–1.23)</td>
<td></td>
<td>P = 0.002 (continuous)</td>
</tr>
</tbody>
</table>
Treatment effect by ejection fraction quartiles
Primary composite total HF hospitalizations and CV death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/Patients</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1903/4796</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=50</td>
<td>512/1208</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>&gt;50–57</td>
<td>536/1287</td>
<td>0.77 (0.57–1.03)</td>
</tr>
<tr>
<td>&gt;57–63</td>
<td>467/1202</td>
<td>0.91 (0.68–1.22)</td>
</tr>
<tr>
<td>&gt;63</td>
<td>388/1099</td>
<td>1.09 (0.80–1.47)</td>
</tr>
</tbody>
</table>
Effect of ARNI across spectrum of HF

The benefits of sacubitril/valsartan are preserved across a wide spectrum of HF, with greatest benefits seen in those with LVEF <60%.

Less benefit in those with LVEF >60% may relate to the specific diagnoses present in this heterogeneous patient population: HCM, amyloid, ischemia.
So, what’s new in 2019?

• Improved understanding of mechanism of action in **chronic** heart failure with reduced ejection fraction

• Expanded role in **acute** heart failure with reduced ejection fraction

• Clarity on the role of ARNI in chronic heart failure with preserved ejection fraction
Conclusions

• Across a wide range of HF presentations, treatment with sacubitril/valsartan is associated with improved clinical outcomes

• A better understanding is now established regarding the mechanism of benefit from sacubitril/valsartan and its role in acute HFrEF

• The success of sacubitril/valsartan (and other drugs) to reduce risk in HFpEF largely depends on the phenotype of the patient being treated
Success of ARNI Continues in 2019: An Update

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Physician, Cardiology Division, Massachusetts General Hospital
Cardiometabolic Faculty, Baim Institute for Clinical Research

JJanuzzi@partners.org  @JJheart_doc