Πώς να εξασφαλίσουμε το μέγιστο όφελος για τον ασθενή με Καρδιακή Ανεπάρκεια;

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Disclosures

Speaker: Gregory Giamouzis, MD, PhD

I have the following potential conflicts of interest to report:

Lecture fees: Astra-Zeneca, Bayer, Boehringer-Ingelheim, Menarini, MSD, Novartis, Pfizer, Servier.

Advisory Boards: Boehringer-Ingelheim, Menarini, MSD, Novartis, Servier.
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Clinical case

78-year-old man

SYMPTOMS:
- orthopnoea and resting dyspnea
- leg edema
- aggravating for 2 weeks
Clinical case-medical history

78-year-old man

MEDICAL HISTORY
- Arterial hypertension (for 7 years)
- **DM type 2 (for 6 years)**
- Anterior MI (5 years ago) with subsequent CABG
- Subsequent HFrEF
- Previous episodes of paroxysmal AF
- **Moderate chronic kidney disease (CKD)**
- Recent LVEF=35%
- NYHA class II
Clinical case—medical history

78-year-old man

CURRENT TREATMENT:
• Rivaroxaban (15 mg od)
• Furosemide (40 mg lately increased to 120 mg od)
• Ramipril (5 mg od)
• Atorvastatin (20 mg od)
• Metoprolol (50 mg bid)
• Metformin (850 mg bid)
Clinical case – Status on admission

78-year-old man

SYMPTOMS:
• orthopnoea and resting dyspnoea
• aggravating for 2 weeks

CLINICAL STATUS:
• BP 115/70 mmHg
• HR 140 bpm, regular
• SAT 86% on air
• pulmonary congestion (confirmed on chest X-ray)
• moderate lower extremity pitting oedema
Clinical case – Status on admission

SYMPTOMS:
• orthopnoea and resting dyspnoea
• aggravating for 2 weeks

LABORATORY TESTS
• sCr=2.10 mg/dl → eGFR 40 mL/min/1.73m²
• Hb 13.2 g/dL
• WBC 5.5 G/L
• NT-proBNP 2830 ng/mL
• CRP negative
Στόχοι θεραπείας ασθενών με ΚΑ βάσει των Κατευθυντήριων Οδηγιών

- Βελτίωση της κλινικής κατάστασης
- Βελτίωση της λειτουργικής ικανότητας
- Βελτίωση της ποιότητας ζωής
- Πρόληψη των επαναλαμβανόμενων νοσηλειών
- Μείωση του κινδύνου θανάτου

Optimization **before** discharge is the **key action** in HF care

**Acute HF**
In-hospital

**Chronic HF**
Outpatient

**Acute phase treatment**
Intravenous therapy

**Transition treatment**
Intravenous therapy
Initiate/up-titration oral GDMT

**Long term treatment**
Optimized oral GDMT

**“Vulnerable phase”**
How can we improve the situation?

- Follow guidelines
- Patient education
- Better coordination between professionals after discharge
- Early initiation of disease modifying therapies
ESC HF Guidelines 2016: Therapeutic Algorithm in Patients with Symptomatic HFrEF

Patients with symptomatic\(^a\) HFrEF\(^b\)

- Therapy with ACE-I\(^c\) and beta-blocker (up-titrate to maximum tolerated evidence-based doses)

  - Still symptomatic and LVEF ≤35%
    - Yes
      - Add MR antagonist\(^d,e\) (up-titrate to maximum tolerated evidence-based dose)
        - Yes
          - Still symptomatic and LVEF ≤35%
            - If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
              - Diuretics to relieve symptoms and signs of congestion
              - ARNI to replace ACE-I

            - Sinus rhythm, QRS duration ≥130msec
              - Evaluate need for CRT\(^i\)

            - Sinus rhythm\(^h\), HR ≥70 beats/min
              - Ivabradine

        - No
          - Able to tolerate ACEI (or ARB)\(^f,g\)

- These above treatments may be combined if indicated

  - Yes
    - Consider digoxin or H-ISDN or LVAD, or heart transplantation
  - No
    - No further action required. Consider reducing diuretic dose

Green indicates a class I recommendation;
Yellow indicates a class IIa recommendation.

Clinical case – Discharge treatment

Discharge clinical status:
BP 109/71 mmHg, HR 82 bpm, no pulmonary congestion, no peripheral edema, exertional dyspnea (NYHA class II), NT-proBNP=1567ng/mL (-50%), sCr=1,69 mg/dl, eGFR=50 ml/min/1,73m²

Scenario A:
- Torasemide (30 mg od)
- Ramipril (5 mg bid)
- Carvedilol (12.5 mg tid)
- Eplerenone (25 mg od)
- Rivaroxaban (15 mg od)
- Atorvastatin (20 mg od)
- Metformin (850 mg bid)

Scenario B:
- Torasemide (30 mg od)
- Sacubitril/Valsartan (24/26 mg bid)
- Carvedilol (12.5 mg tid)
- Eplerenone (25 mg od)
- Rivaroxaban (15 mg od)
- Atorvastatin (20 mg od)
- Metformin (850 mg bid)
Clinical case – Discharge treatment

Discharge clinical status:
BP 109/71 mmHg, HR 82 bpm, no pulmonary congestion, no peripheral edema, exertional dyspnea (NYHA class II), NT-proBNP=1567ng/mL (-50%), sCr=1.69 mg/dl, eGFR=50 ml/min/1.73m²

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Scenario B:
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- Sacubitril/Valsartan (24/26 mg bid)
- Carvedilol (12.5 mg tid)
- Eplerenone (25 mg od)
- Rivaroxaban (15 mg od)
- Atorvastatin (20 mg od)
- Metformin (850 mg bid)
Three-phase terrain of lifetime readmission risk after Heart Failure Hospitalization

- Initial discharge
- Median Time from hospital discharge

- Red: periods of highest risk for readmission
- Green: unavoidable readmissions

“Transition Phase”
“Plateau Phase”
“Palliation and Priorities”

Desai AS and Stevenson LW. Circulation. 2012;126:501-506
Try to initiate an ANRI as soon as possible!!!
Why initiate an ANRI instead of up-titrating the ACE-I?
Primary endpoint:
Death from CV causes or first hospitalization for HF

Hazard ratio = 0.80 (95% CI: 0.73–0.87)  p<0.001

Death from any cause

Hazard ratio = 0.84 (95% CI: 0.76–0.93)  
p<0.001

**ESC-HF guidelines recommendation for sacubitril/valsartan**

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACEi is recommended, in addition to a beta blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A beta blocker is recommended, in addition an ACEi, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACEi and a beta-blocker, to reduce the risk of HF hospitalization and death</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Sacubitril/valsartan is recommended as a replacement for an ACEi to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta-blocker and an MRA</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg b.i.d.*

### 2016 ESC HF guidelines:

*Disease-modifying therapies in HFrEF*

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>Captopril, enalapril, lisinopril, ramipril, trandolapril</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Bisoprolol, carvedilol, metoprolol, nebivolol</td>
</tr>
<tr>
<td>ARBs</td>
<td>Candesartan, valsartan, losartan</td>
</tr>
<tr>
<td>MRAs</td>
<td>Eplerenone, spironolactone</td>
</tr>
<tr>
<td>ARNI</td>
<td>Sacubitril/valsartan</td>
</tr>
<tr>
<td>If inhibitor</td>
<td>Ivabradine</td>
</tr>
</tbody>
</table>

Do we have any evidence for such an early initiation of the ANRI?
Initiation of sacubitril/valsartan in hospitalized patients with HFrEF after hemodynamic stabilization: Primary results of the TRANSITION study
TRANSITION (NCT02661217) is a randomized, parallel, open-label study comparing *pre-* versus *post-discharge* (1–14 days) initiation of sacubitril/valsartan in patients with HFrEF, NYHA II–IV, LVEF ≤40% following hemodynamic stabilization after an episode of ADHF.

TRANSITION protocol allowed the randomization of

1) patients naïve to RAAS inhibitors before admission, and
2) those with newly diagnosed (*de novo*) HFrEF
TRANSITION study design

Patients were stratified into three groups based on their pre-admission treatment status:

(a) receiving an angiotensin-converting enzyme inhibitor (ACEI),

(b) Receiving an angiotensin receptor blocker (ARB),

(c) ACEI/ARB-naïve patients.

Patients were randomized 1:1 within each stratum for initiation of sacubitril/valsartan treatment either pre- or post-discharge.
TRANSITION study design

**Primary endpoint:** the proportion of patients achieving the target dose of 200 mg sacubitril/valsartan b.i.d. at 10 weeks’ post-randomization.

**Secondary endpoints:**
1) **tolerability** of different doses of sacubitril/valsartan (200 mg, 100 mg, any dose) maintained for at least 2 weeks leading to Week 10 after randomization, as well as
2) incidence of **permanent discontinuation** of sacubitril/valsartan due to adverse events (AEs)
TRANSITION study design

N=1002 patients randomized from 156 centers

- Pre-discharge initiation
  - Open-label
    - Sacubitril/valsartan 50 mg b.i.d. → 100 mg b.i.d. → 200 mg b.i.d.
      or
    - Sacubitril/valsartan 100 mg b.i.d. → 200 mg b.i.d.
      as per label and at investigator discretion
  - OMT continued throughout the study (excluding ACEI/ARB)

- Discharge
  - maximum 2 weeks

- Post-discharge initiation
  - Open-label
    - Sacubitril/valsartan 50 mg b.i.d. → 100 mg b.i.d. → 200 mg b.i.d.
      or
    - Sacubitril/valsartan 100 mg b.i.d. → 200 mg b.i.d.
      as per label and at investigator discretion
  - OMT continued throughout the study (excluding ACEI/ARB)

- 1-3 days SCREENING EPOCH

- 10 weeks duration starting at randomization
- 16-week FOLLOW-UP EPOCH
# TRANSITION study: Eligibility criteria

## Table 1. Key eligibility criteria for the patients enrolled in the TRANSITION, PARADIGM-HF, and TITRATION studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>TRANSITION</th>
<th>PARADIGM-HF</th>
<th>TITRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>≥18 years</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td>II-IV</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>≤40%</td>
<td>≤35%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤35%</td>
</tr>
<tr>
<td>Plasma BNP or NT-proBNP levels</td>
<td>No pre-defined entry levels</td>
<td>(BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL) or (BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL and hospitalization for HF within last 12 months)</td>
<td>No pre-defined entry levels</td>
</tr>
<tr>
<td>SBP</td>
<td>≥110 mmHg</td>
<td>≥100 mmHg</td>
<td>≥100 mmHg</td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td>≥30 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Clinical status</td>
<td>Inpatients</td>
<td>Outpatients</td>
<td>Inpatients and outpatients</td>
</tr>
<tr>
<td>Previous ACEI/ARB dose</td>
<td>Variable doses of ACEI/ARB or treatment naïve&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Stable dose of an ACEI/ARB equivalent to enalapril 10 mg/day for at least 4 weeks before the screening</td>
<td>Variable doses of ACEI/ARB or treatment naïve&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> E/e' ≥35%.

<sup>b</sup> None.

<sup>c</sup> In at least 30% of patients in the study.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-discharge initiation n=497</th>
<th>Post-discharge initiation n=496</th>
<th>Total population N=993</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age mean, years</strong></td>
<td>66.7</td>
<td>66.9</td>
<td>66.8</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>372 (74.8%)</td>
<td>373 (75.2%)</td>
<td>745 (75.0%)</td>
</tr>
<tr>
<td><strong>BMI median (min–max), kg/m²</strong></td>
<td>27.9 (17.6–58.8)</td>
<td>28.8 (17.1–53.8)</td>
<td>28.4 (17.1–58.8)</td>
</tr>
<tr>
<td><strong>LVEF mean±SD, %</strong></td>
<td>28.6±7.5</td>
<td>28.9±7.6</td>
<td>28.8±7.6</td>
</tr>
<tr>
<td><strong>SBP mean±SD, mmHg</strong></td>
<td>124±13.8</td>
<td>124±14.1</td>
<td>124±14.0</td>
</tr>
<tr>
<td><strong>eGFR mean±SD, mL/min/1.73 m²</strong></td>
<td>62±20.5</td>
<td>62±19.4</td>
<td>62±20.0</td>
</tr>
<tr>
<td><strong>Ischemic HF etiology, n (%)</strong></td>
<td>219 (44.1)</td>
<td>239 (48.2)</td>
<td>458 (46.1)</td>
</tr>
<tr>
<td><strong>De novo HF, n (%)</strong></td>
<td>148 (29.8)</td>
<td>138 (27.8)</td>
<td>286 (28.8)</td>
</tr>
<tr>
<td><strong>Prior hospitalization for HF, n (%)</strong></td>
<td>237 (47.7)</td>
<td>248 (50.0)</td>
<td>485 (48.8)</td>
</tr>
<tr>
<td><em><em>Median NT-proBNP</em> (Q1–Q3), pg/mL</em>*</td>
<td>1907 (IQR: 948–3826)</td>
<td>1669 (IQR: 706–3599)</td>
<td>1747 (IQR: 846–3735)</td>
</tr>
<tr>
<td><em><em>Median hs-TnT</em> (Q1–Q3), ng/L</em>*</td>
<td>29 (IQR: 18–45)</td>
<td>28 (IQR: 17–44)</td>
<td>29 (IQR: 18–44)</td>
</tr>
</tbody>
</table>

**Medical history, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Pre-discharge initiation n=497</th>
<th>Post-discharge initiation n=496</th>
<th>Total population N=993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>371 (74.6%)</td>
<td>376 (75.8%)</td>
<td>747 (75.2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>225 (45.3%)</td>
<td>233 (47.0%)</td>
<td>458 (46.1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>241 (48.5%)</td>
<td>237 (47.8%)</td>
<td>478 (48.1%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>169 (34.0%)</td>
<td>172 (34.7%)</td>
<td>341 (34.3%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>51 (10.3%)</td>
<td>46 (9.3%)</td>
<td>97 (9.8%)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>38 (7.6%)</td>
<td>50 (10.1%)</td>
<td>88 (8.9%)</td>
</tr>
<tr>
<td>Implantable defibrillator insertion</td>
<td>73 (14.7%)</td>
<td>79 (15.9%)</td>
<td>152 (15.3%)</td>
</tr>
</tbody>
</table>

*at randomization

All p-values for the baseline characteristics are >0.05. BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-TnT, high-sensitivity-Troponin-T; IQR, interquartile range; LVEF, left ventricular ejection fraction; n, number of patients; N, total number of patients; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; SBP, systolic blood pressure; SD, standard deviation
29% of TRANSITION patients had new-onset (de novo) HFrEF; hence, fewer previous HF hospitalizations.
Figure 2. Summary of days from discharge to first dose of sacubitril/valsartan

Safety set N=983
ADHF, acute decompensated heart failure; n, number of patients; N, total number of patients
Figure 4. Predictors for successful sacubitril/valsartan dose up-titration to 200 mg b.i.d.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;65 years vs ≥65 years)</td>
<td>1.42</td>
<td>(1.05, 1.93)</td>
<td>0.0231</td>
</tr>
<tr>
<td>eGFR at baseline (≥60 mL/min/1.73 m² vs &lt;60 mL/min/1.73 m²)</td>
<td>1.52</td>
<td>(1.13, 2.03)</td>
<td>0.0050</td>
</tr>
<tr>
<td>Systolic BP at baseline (≥120 mmHg vs ≥100–&lt;120 mmHg)</td>
<td>1.48</td>
<td>(1.11, 1.97)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Prior heart failure history (No vs Yes)</td>
<td>1.59</td>
<td>(1.15, 2.19)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Medical history of hypertension (Yes vs No)</td>
<td>1.85</td>
<td>(1.31, 2.63)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Atrial fibrillation at baseline (No vs Yes)</td>
<td>1.77</td>
<td>(1.33, 2.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Starting dose of sac/val (100 mg vs 50 mg)</td>
<td>2.41</td>
<td>(1.57, 3.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment (post- vs pre-discharge)</td>
<td>1.20</td>
<td>(0.91, 1.58)</td>
<td>0.1963</td>
</tr>
</tbody>
</table>

For the results shown above, only significant (p<0.05) predictors and treatment group (significant or not) are kept in the model.

b.i.d., twice daily; BP, blood pressure; eGFR, estimated glomerular filtration rate; sac/val, sacubitril/valsartan
TRANSITION: Conclusions –10 week results

- Comparable proportions of patients met the primary and secondary endpoints in the pre- and post-discharge initiation groups
- About half of HFrEF patients stabilized after an ADHF event achieved the target dose of 200 mg sac/val bid within 10 weeks
- At Week 10, more than 86% of patients in both groups were receiving any dose for 2 weeks or longer without interruption
- Incidence of AEs and sacubitril/valsartan discontinuations due to AEs was similar in in-hospital and ambulatory initiation groups

Initiation of sacubitril/valsartan in a wide range of HFrEF patients, early after ADHF event in-hospital or shortly after discharge, was feasible and overall well tolerated
10-week patterns of **NT-proBNP** and high-sensitivity-troponin-T levels after initiation of sacubitril/valsartan, either pre-discharge or early post-discharge, in stabilized HFrEF patients following an ADHF event.
Reduction in NT-proBNP was associated with a reduction in risk of CV mortality or HF hospitalization.

Solid line (± dashed lines) indicates the calculated HR for patient population studied (95% CI)

A 0 value represents no change from baseline, +1 represents a doubling of NT-proBNP at 1 month compared with baseline, and -1 represents a halving of NT-proBNP at 1 month compared with baseline.

CI, confidence interval; CV, cardiovascular; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Change from baseline in NT-proBNP

- **Rapid 28% reduction** from baseline at discharge in **pre-discharge group**
- Once **both groups** were receiving sacubitril/valsartan, the difference between the groups minimized
- **Further reduction** were observed at Weeks 4 and 10 compared with baseline

<table>
<thead>
<tr>
<th>Visit</th>
<th>At discharge</th>
<th>At Week 4</th>
<th>At Week 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-discharge</td>
<td>-28.2*</td>
<td>-25*</td>
<td>-38*</td>
</tr>
<tr>
<td>Post-discharge</td>
<td>-3.4</td>
<td>-22*</td>
<td>-33.7*</td>
</tr>
</tbody>
</table>

\[ p<0.001 \quad p=0.388 \quad p=0.257 \]

*Mixed model with repeated measures; *Change from baseline is \( p<0.05 \)
NT-proBNP early and sustained reduction after sacubitril/valsartan initiation

NT-proBNP (pg/mL) geometric mean by visit and treatment

<table>
<thead>
<tr>
<th>Visit (week)</th>
<th>Pre-discharge group (n=493)</th>
<th>Post-discharge group (n=490)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>1800</td>
<td>1800</td>
</tr>
<tr>
<td>Discharge</td>
<td>1600 (p=0.293)</td>
<td>1600</td>
</tr>
<tr>
<td>Week 4</td>
<td>1400 (p&lt;0.001)</td>
<td>1400</td>
</tr>
<tr>
<td>Week 10</td>
<td>1200 (p&lt;0.001)</td>
<td>1200</td>
</tr>
</tbody>
</table>

Time of optimized HF treatment without sacubitril/valsartan in post-discharge group

p-values indicate the change between randomization and every time point, in each arm

HF, heart failure; n, number of patients; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; OMT, optimized medical therapy

Pascual-Figal D, et al. TRANSITION biomarker poster [Su2183] presented at AHA Congress 2016, Chicago, USA

Safety set
Reductions in hs-TnT levels from baseline were observed in both groups at Weeks 4 and 10.

Change from baseline in hs-TnT

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre-discharge (n=493)</th>
<th>Post-discharge (n=490)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At discharge</td>
<td>-5.4*</td>
<td>-3.9</td>
</tr>
<tr>
<td>At Week 4</td>
<td>-23.3*</td>
<td>-24.9*</td>
</tr>
<tr>
<td>At Week 10</td>
<td>-25.6*</td>
<td>-28.5*</td>
</tr>
</tbody>
</table>

\*Mixed model with repeated measures; \*Change from baseline is \(p < 0.05\)

hs-TnT, high-sensitivity troponin-T; \(n\), number of patients

Pascual-Figal D, et al. TRANSITION biomarker poster [Su2183] presented at AHA Congress 2016, Chicago, USA
Reductions in hs-TnT levels from baseline were observed in both groups

**hs-TnT (ng/L) geometric mean by visit and treatment**

- Pre-discharge group (n=493)
- Post-discharge group (n=490)

**Visit (week)**
- Randomization
- Discharge
- Week 4
- Week 10

- Pre-discharge, n = 462
- Post-discharge, n = 464

**Time of optimized HF treatment without sac/val in post-discharge group**

*p-values indicate the change between randomization and every time point, in each arm*

**hs-TnT**, high-sensitivity troponin-T; n, number of patients

Conclusions

- Within a few days of in-hospital initiation of sacubitril/valsartan, NT-proBNP levels in the pre-discharge group decreased significantly, compared with standard of care HF medical treatment in the post-discharge group.

- Once both groups were receiving sacubitril/valsartan, no further difference between the groups was observed. Further reduction of NT-proBNP levels were observed at Weeks 4 and 10 compared with baseline.

- In-hospital initiation of sacubitril/valsartan was associated with a significant reduction in hs-TnT levels from baseline to discharge. Further reductions from baseline were observed in both groups at Weeks 4 and 10.

- Previously reported primary results of TRANSITION showed that initiation of sacubitril/valsartan shortly after an ADHF event is feasible and well tolerated.

In-hospital initiation of sacubitril/valsartan is associated with early and sustained improvements in biomarkers of cardiac wall stress and myocardial injury, indicating pathophysiological benefits in a wide range of HFrEF patients.

ADHF, acute decompensated heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hs-TnT, high-sensitivity-troponin-T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Is there such evidence in CKD patients?
Renal Effects and Associated Outcomes During Angiotensin-Nephrilysin Inhibition in Heart Failure

Kevin Damman, MD, Ph.D., Mauro Gori, MD, Brian Claggett, PhD, Pardeep S. Jhund, MB, PhD, Michele Senni, MD, Martin P. Leskowitz, MD, Margaret F. Prescott, PhD, Victor C. Shi, MD, Jean L. Rouleau, MD, Karl Swedberg, MD, PhD, Michael R. Zile, MD, Milton Packer, MD, Alshay S. Desai, MD, MPH, Scott D. Solomon, MD, John J.V. McMurray, MD

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the renal effects of sacubitril/valsartan in patients with heart failure and reduced ejection fraction.

BACKGROUND Renal function is frequently impaired in patients with heart failure with reduced ejection fraction and may deteriorate further after blockade of the renin-angiotensin system.

METHODS In the PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, 8,399 patients with heart failure with reduced ejection fraction were randomized to treatment with sacubitril/valsartan or enalapril. The estimated glomerular filtration rate (eGFR) was available for all patients, and the urinary albumin/creatinine ratio (UACR) was available in 1872 patients, at screening, randomization, and at fixed time intervals during follow-up. We evaluated the effect of study treatment on change in eGFR and UACR, and on renal and cardiovascular outcomes, according to eGFR and UACR.

RESULTS At screening, the eGFR was 70 ± 20 ml/min/1.73 m² and 2,745 patients (33%) had chronic kidney disease; the median UACR was 1.0 mg/mmol (interquartile range: 0.4 to 3.2 mg/mmol) and 24% had an increased UACR. The decrease in eGFR during follow-up was less with sacubitril/valsartan compared with enalapril (−1.61 ml/min/1.73 m²/year; [95% confidence interval: −1.77 to −1.44 ml/min/1.73 m²/year] vs. −2.04 ml/min/1.73 m²/year [95% CI: −2.21 to −1.88 ml/min/1.73 m²/year]; p < 0.001) despite a greater increase in UACR with sacubitril/valsartan than with enalapril (1.20 mg/mmol [95% CI: 1.04 to 1.36 mg/mmol] vs. 0.90 mg/mmol [95% CI: 0.77 to 1.03 mg/mmol]; p < 0.001). The effect of sacubitril/valsartan on cardiovascular death or heart failure hospitalization was not modified by eGFR, UACR (p interaction = 0.70 and 0.34, respectively), or by change in UACR (p interaction = 0.38).

CONCLUSIONS Compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved cardiovascular outcomes, even in patients with chronic kidney disease, despite causing a modest increase in UACR. (J Am Coll Cardiol HF 2018; [pii: -] © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
Change in estimated glomerular filtration rate (eGFR)

Urinary albumin to creatinine ratio (UACR) levels over time

Primary outcome by treatment group and CKD status at screening

![Graph showing cumulative probability of combined endpoint over days since randomization for different treatment groups.]

Enalapril, No CKD
Enalapril, CKD
Sacubitril/Valsartan, No CKD
Sacubitril/Valsartan, CKD

Days since Randomization
Cumulative Probability of Combined Endpoint

Is there such evidence in diabetic patients?
Influence of Sacubitril/Valsartan on Glycemic Control in Patients with Heart Failure and Diabetes Mellitus: The PARADIGM-HF Trial

Jelena P. Seferovic, M.D.¹, Brian Claggett, Ph.D¹, Sara B. Seidelmann, M.D.¹, Ellen W. Seely, M.D.², Milton Packer, M.D.³, Michael R. Zile, M.D.⁴, Jean L. Rouleau, M.D.⁵, Karl Swedberg, M.D.⁶, Martin Lefkowitz, M.D.⁷, Victor C. Shi, M.D.⁷, Akshay S. Desai, M.D.¹, John J. V. McMurray, M.D.⁸, Scott D. Solomon, M.D.¹

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Influence of Sacubitril/Valsartan on Glycemic Control in Patients with Heart Failure and Diabetes Mellitus: The PARADIGM-HF Trial

Influence of Sacubitril/Valsartan on Glycemic Control in Patients with Heart Failure and Diabetes Mellitus: The PARADIGM-HF Trial

New Insulin Use

HR = 0.71 (0.56-0.90); p=0.005

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Enalapril 1490</th>
<th>Sacubitril/Valsartan 1550</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1286</td>
<td>1377</td>
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<td>837</td>
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<tr>
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<td>284</td>
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</table>

Seferovic JP, et al. *Lancet Diabetes Endocrinol* 2017 accepted for publication
Proposed mechanisms by which ARNIs may lead to improved glycemic control

Sacubitril/Valsartan

- Neprilysin inhibition
  - ↑ Natriuretic peptides
    - ↑ Insulin sensitivity
    - ↑ Lipid mobilization
    - ↑ Insulin metabolism
    - ↑ Adiponectin release
    - ↓ Blood glucose levels
    - ↑ Postprandial lipid oxidation
    - ↑ Muscular oxidative capacity
  - ↑ Bradykinin
    - ↑ Insulin sensitivity
    - Attenuated lipolysis
  - ↑ GLP-1
    - ↑ Insulin sensitivity
  - ↑ Skeletal muscle cGMP
    - Facilitated lipolysis
    - Vasodilation
  - ↓ DPP-4 activity
    - ↑ beta-cell function

AT\textsubscript{1}-receptor blockade

- ↑ Insulin sensitivity

Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial

Milton Packer, Brian Claggett, Martin P Lefkowitz, John V McMurray, Jean L Rouleau, Scott D Solomon, Michael R Zile
Neprilysin inhibition has favourable effects on experimental diabetic nephropathy. We sought to assess the effects of neprilysin inhibition on the course of renal function in patients with type 2 diabetes.

Milton Packer, Brian Claggett, Martin P Lefkowitz, John V McMurray, Jean L Rouleau, Scott D Solomon, Michael R Zile
Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial

Milton Packer, Brian Claggett, Martin P Lefkowitz, John V McMurray, Jean L Rouleau, Scott D Solomon, Michael R Zile

Methods In this secondary intention-to-treat analysis of the PARADIGM-HF trial, we assessed the change in estimated glomerular filtration rate (eGFR) over a 44-month follow-up period in patients with (n=3784) and those without (n=4615) diabetes.

Change in eGFR in patients with and those without diabetes

![Graph showing change in eGFR over years for patients with and without diabetes.](image)

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Years since randomisation</th>
</tr>
</thead>
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<tr>
<td>Diabetes</td>
<td>3123</td>
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<tr>
<td></td>
<td>1</td>
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<tr>
<td>No diabetes</td>
<td>2769</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td></td>
<td>2</td>
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<tr>
<td>No diabetes</td>
<td>1339</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1006</td>
</tr>
</tbody>
</table>

Legend:
- Blue line: No diabetes
- Red line: Diabetes
Change in eGFR in patients with and those without diabetes by treatment assignment

Clinical case – 1-Week outpatient follow-up

Discharge clinical status:
BP 109/71 mmHg, HR 82 bpm, no pulmonary congestion, no peripheral edema, exertional dyspnea (NYHA class II), NT-proBNP=1567ng/mL (-50%), sCr=1,69 mg/dl, eGFR=50 ml/min/1,73m²

DISCHARGE TREATMENT:
• Torasemide (30 mg od)
• **Ramipril (5 mg bid)** - - - -> Sacubitril/Valsartan (24/26 mg bid)
• Carvedilol (12.5 mg tid)
• Eplerenone (25 mg od)
• Rivaroxaban (15 mg od)
• Atorvastatin (20 mg od)
• Metformin (850 mg bid)

Next steps:
• Check BP, sCr, K⁺ within a week (2-week telephone schedule)
• Sacubitril/Valsartan (24/26 mg bid)- - - - -> Sacubitril/Valsartan (49/51 mg bid) (4-week visit schedule)
Initiation/uptitration of ARNI according to previous treatment

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

Michele Senni¹, John J.V. McMurray², Rolf Wachter³, Hugh F. McIntyre⁴,

- Initiation/uptitration of sacubitril/valsartan from 50 mg to 200 mg twice daily over 3 or 6 weeks had a tolerability profile in line with other HF treatments.
- No difference in adverse events between the 2 titration regimes.
- In the low-dose ACEI/ARB group, more gradual initiation/uptitration is required to maximize the attainment of target dose.

<table>
<thead>
<tr>
<th>Study medication</th>
<th>Low-dose RAAS inhibition stratum</th>
<th>High-dose RAAS inhibition stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors (ACEIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Captopril</td>
<td>≤ 100 mg</td>
<td>&gt;100 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>≤ 20 mg</td>
<td>&gt; 20 mg</td>
</tr>
<tr>
<td>Imidapril</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>≤ 4 mg</td>
<td>&gt; 4 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>&lt; 20 mg</td>
<td>&gt; 20 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>≤ 5 mg</td>
<td>&gt; 5 mg</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>≤ 2 mg</td>
<td>&gt; 2 mg</td>
</tr>
<tr>
<td>Zofenopril</td>
<td>≤ 30 mg</td>
<td>&gt; 30 mg</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers (ARBs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>≤ 16 mg</td>
<td>&gt; 16 mg</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>≤ 400 mg</td>
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<tr>
<td>Irbesartan</td>
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<tr>
<td>Telmisartan</td>
<td>≤ 40 mg</td>
<td>&gt; 40 mg</td>
</tr>
<tr>
<td>Valsartan</td>
<td>≤ 160 mg</td>
<td>&gt;160 mg</td>
</tr>
</tbody>
</table>
What about functional Mitral Regurgitation?
ARNIs for Functional Mitral Regurgitation: The PRIME Study

What about need for diuretics?
Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial

Orly Vardeny¹,²*, Brian Claggett³, Jessica Kachadourian⁴, Akshay S. Desai³, Milton Packer⁵, Jean Rouleau⁶, Michael R. Zile⁷, Karl Swedberg⁸, Martin Lefkowitz⁴, Victor Shi⁴, John J.V. McMurray⁹, and Scott D. Solomon³

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Received 16 August 2018; revised 21 November 2018; accepted 24 November 2018
Clinical case – 4-Week outpatient follow-up

Outpatient visit - 4 week post discharge
Clinical status: BP=99/62 mmHg, HR=62 bpm, no pulmonary congestion, no peripheral oedema exertional dyspnoea (NYHA class II), K+=5.0mEq/L sCr=1.63 mg/dl, eGFR=52 ml/min/1.73m²

CURRENT TREATMENT:
• Torasemide (30 mg od) → Torasemide 20 mg od
• Sacubitril/Valsartan (24/26 mg bid) → No change!
• Carvedilol (12.5 mg tid)
• Eplerenone (25 mg od)
• Rivaroxaban (15 mg od)
• Atorvastatin (20 mg od)
• Metformin (850 mg bid)

Next steps:
• 6-week visit schedule
• Sacubitril/Valsartan (24/26 mg bid) - - - - - - - → Sacubitril/Valsartan (49/51 mg bid)
Clinical case – 6-Week outpatient follow-up

Outpatient visit - 4 weeks post discharge
Clinical status: BP 109/68 mmHg, HR 60 bpm, no pulmonary congestion, no peripheral oedema exertional dyspnoea (NYHA class I-II), K⁺=5.1mEq/L sCr=1,52 mg/dl, eGFR=58 ml/min/1,73m²

CURRENT TREATMENT:
• Torasemide (20 mg od)
• Sacubitril/Valsartan (24/26 mg bid) → 49/51 mg bid
• Carvedilol (12.5 mg tid)
• Eplerenone (25 mg od)
• Rivaroxaban (15 mg od)
• Atorvastatin (20 mg od)
• Metformin (850 mg bid)

Next steps:
• 8-week visit schedule
• Sacubitril/Valsartan (97/103 mg bid)
• Torasemide 10mg od
Take home messages
Take home messages

- *Early initiation* of sacubitril/valsartan *shortly after discharge*, is feasible and overall very well tolerated.

- *Younger patients* with *fewer comorbidities, higher systolic* blood pressure or *newly diagnosed HF* are more likely to tolerate the up-titration of sacubitril/valsartan to the target dose of 200 mg bid.

- eGFR decreases *less* in patients receiving neprilysin inhibition in addition to a RAAS blocker, compared with a RAAS blocker alone.

- The relative risk reduction in CV events is similar in patients with or without *CKD or DM* at baseline and the renal safety profile of sacubitril/valsartan is more favorable than that of enalapril.

- Sacubitril/valsartan reduces functional mitral regurgitation and the need for diuretics more than enalapril or valsartan alone.
Thank You

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February 22nd 2019, Thessaloniki, Greece
grgiamouzis@med.uth.gr