ROL DEL LCZ696 EN EL MANEJO DE LA INSUFICIENCIA CARDIACA

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Objectives

• To revisit and review key neurohormonal pathways in heart failure

• To understand the potential role for neprilysin inhibitors in heart failure

• To review the recent literature and clinical trials of neprilysin inhibitors, including the PARADIGM HF study
Disclosures

- Primary investigator PARADIGM-HF
- Honorarium: Novartis
Trend in HF

• Reduction in HF mortality (12%)
• Increase aging population
• Higher incidence of cardiac risk factors
• Higher prevalence of HF

Source: Framingham, Olmstec County, Canada (ICES)
HF Outcomes – Unchanged Despite Advances In Medical Therapy

– The average lifespan of HF patients is 5.5 years\(^1\)
– Approximately 1 in 4 HF patients is readmitted to the hospital within 1 year of discharge\(^2\)
– Prognosis for HF patients remains poor with only slight improvements in overall mortality\(^3\)

*\(p<0.1/**p<0.02\)
Each hospitalization has a major impact on patient survival

Go AS et al., Circulation, 2013, 127, e6–e245

50% of the patients will die within 2.5 years of first hospitalization

Setoguchi S et al., Am Heart J, 2007 Aug, 154(2), 203-205
1/3 of patients have no follow-up and they have the worst outcomes as soon as 30 days.
Projection of cost in US

Heindereich Circ Heart Failure 2013
Cost

• 1%-2% of global health expenditures in developed countries
• Hospitalizations
• Patients with comorbidities (diabetes)
Model For Future Disease Management Of HF

From this

Heart Failure Clinic

Patient with Heart Failure

Primary Care Provider

To this!

HF Patient

Heart Failure Clinic

Other Care Provider

Family and community

Primary Care Provider
Neurohormonal Activation and Rationale For Standard Therapy for Systolic Heart Failure
Neurohormonal activation is a central mechanism of progressive HF

- Initially supports the circulation
- Ultimately highly negative impact
Decline In Systolic Function Leads To Activation Of Three Major Neurohormonal Systems

- **Ang**=angiotensin; AT1R=angiotensin II type 1 receptor; HF=heart failure; NPs=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system
Neurohormonal blockade in HF – historical paradigm

Angiotensinogen → Renin → Angiotensin I → Angiotensin II

AT1 Receptor stimulation

ACE Inhibitors

Angiotensin receptor blockers

Aldosterone Release

Aldosterone Antagonists

Vasoconstriction, Na retention, myocyte hypertrophy and apoptosis, endothelial dysfunction, sympathetic activation, free radical generation, etc.
Good…. but not perfect

Guideline-Directed Medical Therapy

Residual risk still exists

HF mortality remains high (50% over 5 years)
Other players

Natriuretic peptides
  + Bradykinin
  + Adrenomedulin

Vasodilatation
  ↓ Blood pressure
  ↓ Sympathetic tone
  ↓ Aldosterone levels
  ↓ Fibrosis
  ↓ Hypertrophy
  ↑ Natriuresis/diuresis

Neprilysin
  • Neutral endopeptidase
  • Breaks down vasoactive peptides
  • Contributes to hypertension and HF progression

Inactive Peptides
Neurohormonal blockade in HF – revisited

- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin → Angiotensin I
- ACE
- Bradykinin

Active natriuretic peptides
- Neprilysin
- Neprilysin inhibitor

Inactive natriuretic peptides
- Angiotensin receptor blockers

AT1 Receptor stimulation
- Aldosterone Release

Aldosterone Antagonists

Vasoconstriction, Na retention, myocyte hypertrophy and apoptosis, endothelial dysfunction, sympathetic activation, free radical generation, etc.
NEP Inhibition Must Be Accompanied By Simultaneous RAAS Blockade

NEP metabolizes Ang I and Ang II via several pathways\textsuperscript{1,2}

Inhibition of NEP alone is insufficient as it is associated with an increase in Ang II levels, counteracting the potential benefits of NEP inhibition\textsuperscript{2}

NEP inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT\textsubscript{1} receptor blockade)\textsuperscript{2}

\textbullet\ ACE=angiotensin converting enzyme; AT1 = angiotensin II type 1; Ang=angiotensin; NEP=neprilysin; RAAS=renin angiotensin aldosterone system
\textbullet\ 1. Von Lueder et al. Circ Heart Fail 2013;6:594–605;
\textbullet\ 2. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9
Have neprilysin inhibitors been studied before?

- **Omapatrilat**
  - combined neprilysin inhibitor/ACEi/aminopeptidase P

- Studied in HF, hypertension

- Unacceptably high incidence of angioedema
  - 3-fold increase in risk
  - Increased life-threatening episodes

Kostis et al, OCTAVE Trial, Am J Hypertension 2004
Packer et al, OVERTURE Trial, Circulation 2002
The omapatrilat group had a 9% lower risk of cardiovascular death or hospitalization (p=0.024) and a 6% lower risk of death (p=0.339).

Omapatrilat ↓ the risk of death and hospitalization in chronic HF but was not more effective than ACE inhibition alone in reducing the risk of a primary clinical event.
OCTAVE: Incidence Of Angioedema

N=25,302 patients with hypertension

- 2.17% for Omapatrilat
- 0.68% for Enalapril

Inhibition of:
1. Neprilysin
2. ACE
3. Aminopeptidase

Angioedema

LCZ696
- A novel ARNI compound -

Complex with two active components:

- AHU377 pro-drug; further metabolized to the neprilysin inhibitor LBQ657
  
  *Plus*

- Valsartan; angiotensin receptor (AT1) blocker
Neurohormonal blockade in HF – revisited again

Angiotensinogen → Renin → Angiotensin I → Angiotensin II

Angiotensin II → AT1 Receptor stimulation → Vasoconstriction, Na retention, myocyte hypertrophy and apoptosis, endothelial dysfunction, sympathetic activation, free radical generation, etc

ACE Inhibitors

Angiotensin receptor blockers

Neprilysin → LCZ696 → Inactive natriuretic peptides → Reduced NO and vasodilating PGs

Bradykinin → Reduced NO and vasodilating PGs

Aldosterone Release → Aldosterone Antagonists
LCZ696 Simultaneously Enhances The Beneficial Effects Of The NP System While Blocking Detrimental Effects Of The RAAS

- ANP: atrial natriuretic peptide; Ang: angiotensin; AT1 = angiotensin II type 1; BNP=B-type natriuretic peptide; cGMP=cyclic guanosine monophosphate; CNP=C-type natriuretic peptide; GTP=guanosine triphosphate; NEP=neprilysin; NP=natriuretic peptide; NPR=natriuretic peptide receptor; RAAS=renin-angiotensin-aldosterone system

Simultaneous Inhibition Of Neprilysin And Suppression Of The RAAS With LCZ696 Has Complementary Effects

LCZ696

Enhancing cGMP-mediated effects of natriuretic peptides

- Vasodilation
- Natriuretic and diuretic effects
- Proliferation
- Hypertrophy
- SNS outflow/sympathetic tone
- Aldosterone secretion
- Detrimental effects of vascular remodeling

Suppressing RAAS-mediated effects

- Vasoconstriction
- Sodium and water retention
- Ventricular hypertrophy/remodeling
- Aldosterone secretion
- Cardiac fibrosis
- Sympathetic tone
- Systemic vascular resistance

- cGMP=cyclic guanosine monophosphate; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system
Early Experience with LCZ696: HF with Preserved EF (PARAMOUNT Study)

Phase II trial
300 pts with HFP EF

Randomized 1:1 LCZ696 vs valsartan

LCZ696 had greater short-term reduction in NT pro BNP, Left atrial size, improvement in NYHA class
Now on to HF with reduced EF…

• The PARADIGM HF Study
  – Designed to assess whether the long-term effects of LCZ696 were superior to an ACEi in reducing morbidity and mortality
  – Powered to detect difference in mortality
## Patient Population

### Inclusion Criteria

- Chronic HF NYHA FC II–IV with LVEF ≤40% → 35%
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks’ stable treatment with an ACEI or an ARB, and a beta-blocker
- Aldosterone antagonist encouraged (with stable dose for ≥4 weeks)

### Key Exclusion Criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m² or >35% drop in eGFR prior to randomization
- Serum potassium >5.4 mmol/L prior to randomization
- SBP <95 mmHg prior to randomization
- Current acute decompensated HF
- Severe pulmonary disease
- Recent MI, stroke, CV surgery, PCI

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McMurray et al. Eur J Heart Fail 2013
PARADIGM-HF: Study Design

**Single-blind active run-in period**
- **Enalapril 10 mg BID**
- **LCZ696 100 mg BID**
- **LCZ696 200 mg BID**

**Randomization**
- n=8442

**Double-blind Treatment period**
- **LCZ696 200 mg BID**
- **Enalapril 10 mg BID**

On top of standard HFrEF therapy (excluding ACEIs and ARBs)

**Note:** Health Canada approved corresponding doses for LCZ696 are as follows:
- LCZ696 100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
- LCZ696 200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

- Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; † 200 mg TDD; ‡ 400 mg TDD; § 20 mg TDD.
Paradigm HF Trial

• 8442 patients randomized to
  – Enalapril 10mg bid vs LCZ696 200mg bid

• Median follow-up 27 months

• Outcomes:
  – CV death or HF hospitalization
  – CV death
  – HF hospitalization
  – All cause death
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy, n (%)</strong></td>
<td>2506 (59.9)</td>
<td>2530 (60.1)</td>
</tr>
<tr>
<td><strong>LV ejection fraction, %</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2998 (71.6)</td>
<td>2921 (69.3)</td>
</tr>
<tr>
<td>III</td>
<td>969 (23.1)</td>
<td>1049 (24.9)</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>NT pro-BNP, pg/mL (IQR)</strong></td>
<td>1631 (885–3154)</td>
<td>1594 (886–3305)</td>
</tr>
<tr>
<td><strong>BNP, pg/mL (IQR)</strong></td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td><strong>Treatments at randomization, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>3363 (80.3)</td>
<td>3375 (80.1)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1223 (29.2)</td>
<td>1316 (31.2)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>2271 (54.2)</td>
<td>2400 (57.0)</td>
</tr>
<tr>
<td>ICD</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
<tr>
<td>CRT</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
</tbody>
</table>
Primary endpoint:

Death from CV causes or first hospitalization for HF

![Graph showing cumulative probability over time with two lines representing Enalapril and LCZ696. The hazard ratio is 0.80 (95% CI: 0.73–0.87) with p<0.001. The NNT* is 21 patients.]

No at risk
LCZ696  |  Enalapril
---|---
4187 | 4212
3922 | 3883
3663 | 3579
3018 | 2922
2257 | 2123
1544 | 1488
896  | 853
249  | 236

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

NNT*=21 patients
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with SBP &lt;90 mmHg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Elevated serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dL</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dL</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Elevated serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/L</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong> (adjudicated by a blinded expert committee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE.
PARADIGM-HF: AE Leading To Permanent Drug Study Discontinuation

Fewer patients in the LCZ696 group than in the enalapril group discontinued study drug due to an AE (10.7 vs. 12.3%; p=0.03)

LCZ696 prevents disease progression

• Subanalysis of PARADIGM HF
  – LCZ696 reduced ED visits, hospitalization, inotrope use
  – Less intensification of HF therapy
  – Lower troponin and NT pro BNP levels
  – Improved symptom scores

Packer et al Circulation 2015
TITRATION Study: Design

Randomization
1:1

Open-label run-in period

[Flowchart showing the study design with dates and doses]

Primary endpoint: safety profile and tolerability

Target patient population:
Inpatients* or outpatients with CHF (NYHA Class II–IV; LVEF ≤35%)
Both naïve to or on any dose of ACEI/ARBs‡
Stratified 1:1 based on level of RAS inhibition

Note: Health Canada approved corresponding doses for LCZ696 are as follows:
LCZ696 50 mg: 24.3 mg sacubitril / 25.7 mg valsartan
LCZ696 100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
LCZ696 200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

- *Patients enrolled as hospital in-patients will be limited to 1/3 of the total randomized study sample;
- ‡Outpatients on a stable ACEI/ARB dosage or not exposed to ACEIs/ARBs for at least 2 weeks prior to screening.
TITRATION Study: Treatment Success

Overall treatment success (excluding non-AE related discontinuations)¹

- High RASi dose: OR=0.65 (95% CI 0.41–1.05), p=0.08
- Low RASi dose: OR=0.91 (95% CI 0.45–1.83), p=0.78

Treatment success by RASi stratum²

- High RASi dose: OR=0.50 (95% CI 0.26–0.94), p=0.03
- Low RASi dose: OR=0.91 (95% CI 0.45–1.83), p=0.78

Conservative regimen
Condensed regimen

Treatment success was defined as achievement and maintenance of LCZ696 200 mg b.i.d without down-titration or dose interruption over 12 wks.

- High RASi dose=>10 mg enalapril/day, or equivalent, at screening; low RASi dose= ≤10 mg enalapril/day, or equivalent, at screening
- AE=adverse event; CI=confidence intervals; OR=odds ratio; RASi=renin-angiotensin system inhibitor
- 3. Novartis Data on File: TITRATION study B2228
TITRATION Study: LCZ696 Had An Acceptable Safety Profile Regardless Of Up-titration Regimen Or RASi Dose At Screening

- High RASi dose: 
  - Hypotension: 4.2% (p=0.657)
  - Renal dysfunction: 5.5% (p=0.371)
  - Hyperkalemia: 7.1% (p=0.312)
  - Angioedema: 6.7%

- Low RASi dose: 
  - Hypotension: 11.3% (p=0.353)
  - Renal dysfunction: 10.2% (p=0.492)
  - Hyperkalemia: 8.7% (p=0.225)
  - Angioedema: 4.8%

High RASi dose=>10 mg enalapril/day, or equivalent, at screening; low RASi dose= ≤10 mg enalapril/day, or equivalent, at screening.

- 1. Senni et al. Abstract accepted for presentation at ESC Heart Failure 2015b (1281); 2. Novartis Data on File: TITRATION study B2228
TITRATION Study: Summary

– LCZ696 demonstrated an acceptable safety and tolerability profile

– After excluding non-AE or death-related discontinuations, ≥78% of patients achieved and maintained the target dose of LCZ696 200 mg b.i.d for 12 weeks$^{1,2}$

– **Gradual titration over 6 weeks in patients taking low doses of, or naïve to, RASi prior to LCZ696 initiation, may further increase the chances of achieving treatment success$^1$**

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- AE=adverse event; b.i.d.= twice daily; RASi=renin-angiotensin system inhibitor; SBP=systolic blood pressure
- 1. Senni et al. Abstract accepted for presentation at ESC Heart Failure 2015a + poster P1795;
  2. Senni et al. Abstract accepted for presentation at ESC Heart Failure 2015b (1281);
Too good to be true?

• Single trial
• 12% patients withdrew during run-in phase
  – Target doses may not be achievable in real world
• Low baseline use of ICD and CRT
  – May mitigate benefit with increase device use
• Higher incidence of hypotension vs. ACEi
• Not representative of patients with more advanced HF
Concerns

• Trial no dot represent real-world patients
  – Only 310 pts (7.4%) on LCZ from North America
  – Only 213 pts (5.1%) on LCZ were Black
  – Only 879 pts (21%) on LCZ were Female
• Chronic HF
• Replacement for ACEI/ARB
  – Little evidence for de novo HF
  – Indicated for those on ACEI/ARB and increased BNP
  – Limited by hypotension, potassium, creatinine (< 5.2 mmol/L and eGFR ≥ 30 mL/min)
  – Wash out period >36 hrs (ACEI)
  – Two titrations (50, 100, 200) for 6-12 weeks
TM

ENTRESTO™ (sacubitril/valsartan) film-coated tablets:

• 24.3mg sacubitril/ 25.7mg valsartan  
  – Equivalent to 40mg valsartan monotherapy

• 48.6mg sacubitril/ 51.4mg valsartan  
  – Equivalent to 80mg valsartan monotherapy
  – Equivalent to 100mg of LCZ696 in the Paradigm HF study

• 97.2mg sacubitril/ 102.8mg valsartan  
  – Equivalent to 160mg valsartan monotherapy
  – Equivalent to 200mg of LCZ696 in the Paradigm HF study

50 MG

100 MG

200 MG
In stable patients whose baseline systolic blood pressure, serum potassium and renal function are at acceptable levels sacubitril/valsartan may be initiated:

- The usual recommended starting dose is one tablet of 48.6mg sacubitril/51.4mg valsartan taken twice daily\(^1\). (100 mg)
- The target dose is one tablet of 97.2mg sacubitril/102.8mg valsartan taken twice daily\(^2\).

A starting dose of one tablet of 24.3mg sacubitril/25.7mg valsartan taken twice daily should be considered in certain patients: (50 mg)

- Patients on less than guideline-recommended doses of ACEi or ARB prior to initiation of sacubitril/valsartan
- Patients who have risk factors for hypotension, including patients ≥75 years old and patients with low systolic blood pressure.

\(^1\)Equivalent to starting dose of 100mg LCZ696 in the Paradigm HF trial. \(^2\) Equivalent to 200mg of LCZ696 in the Paradigm HF trial.
DOSAGE AND ADMINISTRATION
SPECIAL POPULATIONS

• Renal impairment
  – No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m²) or moderate (eGFR 30-60 mL/min/1.73 m²) renal impairment.
  – Since there are no adequate data in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), sacubitril/valsartan use is not recommended in these patients.

• Hepatic impairment
  – No dose adjustment is required when administering sacubitril/valsartan to patients with mild hepatic impairment (Child-Pugh A classification).
  – In patients with moderate hepatic impairment (Child-Pugh B classification), a starting dose of one tablet of 24.3mg sacubitril/25.7 mg valsartan taken twice daily is recommended.
  – No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore, use of sacubitril/valsartan in these patients is not recommended.
DOSAGE AND ADMINISTRATION
SPECIAL POPULATIONS

• Geriatrics
  – No dosage adjustment is required in patients over 65 years. However, sacubitril/valsartan has been studied in a limited number of patients above the age of 80 years.
  – In patients ≥ 75 years old, a starting dose of one tablet of 24.3mg sacubitril/25.7mg valsartan taken twice daily should be considered.
DRUG INTERACTIONS

• Both LBQ657, the active metabolite of sacubitril, and valsartan are OATP1B1, OATP1B3 and OAT3 substrates. Valsartan is also a MRP2 substrate. Therefore, co-administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657, or valsartan, respectively.

• In vitro studies indicate that the potential for CYP 450-based drug interactions is low since there is limited metabolism of sacubitril/valsartan by the cytochrome P450 system. Sacubitril/valsartan does not induce or inhibit CYP isozymes itself.

• No clinically meaningful drug-drug interaction was observed with co-administration of sacubitril/valsartan with digoxin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, or intravenous nitroglycerin in dedicated interaction studies.
## ESTABLISHED or POTENTIAL DRUG-DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Proper name</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>T</td>
<td>In vitro data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril/valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of sacubitril/valsartan increased the Cmax of atorvastatin and its metabolites by up to 2-fold, and AUC by up to 1.3-fold.</td>
<td>Caution should be exercised upon co-administration of sacubitril/valsartan with statins, especially simvastatin, a sensitive OATP1B1/1B3 substrate. Downward dose adjustment of simvastatin and atorvastatin may be considered with such co-administration.</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>CT</td>
<td>Administration of a single dose of 50 mg sildenafil to sacubitril/valsartan at steady-state (194.4 mg sacubitril / 205.6 mg valsartan OD for 5 days) was associated with additional blood pressure reduction (~5/4 mmHg).</td>
<td>Caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with sacubitril/valsartan.</td>
</tr>
<tr>
<td>Non-Steroidal Anti-Inflammatory Agents (NSAID), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)</td>
<td></td>
<td>Especially in elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of sacubitril/valsartan and NSAID may lead to an increased risk of worsening of renal function.</td>
<td>Monitoring of renal function is mandatory when initiating or modifying the treatment in patients on sacubitril/valsartan who are taking NSAID concomitantly. In general, avoid such combined use.</td>
</tr>
</tbody>
</table>

Legend: CT = Clinical Trial; T = Theoretical
Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction

Patient with LVEF <40%

NYHA I: SR, HR ≥ 70 bpm
- Continue triple therapy

NYHA II-IV: SR with HR < 70 bpm or AF or pacemaker
- ADD Ivabradine and SWITCH ACEi or ARB to LCZ696 for eligible patients

NYHA II-IV:
- SWITCH ACEi or ARB to LCZ696 for eligible patients

NYHA I or LVEF > 35%
- NYHA I-III and LVEF ≤ 35%
- NYHA IV

Continue present management
- Refer to ICD/CRT algorithm
- Consider:
  - Hydralazine/nitrates
  - Referral for advanced HF therapy (mechanical transplant)
  - Advance HF referral

Reassess every 1-3 years or with clinical status change

Consider LVEF reassessment every 1-5 years

Reassess as needed according to clinical status

Non-pharmacologic therapies (teaching self-care, exercise)
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