SDSHP ANNUAL MEETING CLINICAL PEARLS

APRIL 7TH, 2017

SACUBITRIL/VALSARTAN (ENTRESTO)

A NOVEL THERAPY FOR HEART FAILURE

DISCLOSURE

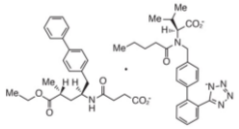
I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation.

LEARNING OBJECTIVES

- **Pharmacist:**
  - Explain the two mechanisms by which ANRIs work
  - Identify four significant side effects for sacubitril/valsartan
- **Technician:**
  - Identify the primary indication for sacubitril/valsartan
  - List the available product forms and strengths for sacubitril/valsartan

MEDICINAL CHEMISTRY

Entresto® = sacubitril/valsartan (formerly LCZ696)



Sacubitril (AHU377) Valsartan

Drug formulation

- Ionic complex (1:1) of sacubitril and valsartan
- Sacubitril undergoes metabolic conversion to active form

MECHANISM OF ACTION

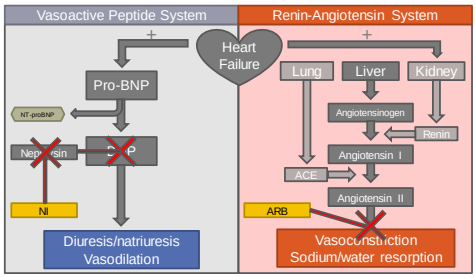
Valsartan

- Antagonist of angiotensin II type-1 (AT1) receptor

Sacubitril (AHU377)

- Metabolized by hepatic carboxylesterase1 to LBQ657
  - Only known active metabolite
- Selective inhibitor of neprilysin
  - Neprilysin degrades atrial natriuretic peptide (ANP), **b-type natriuretic peptide (BNP)**, and c-type natriuretic peptide (CNP)
  - Also degrades angiotensin

MECHANISM AND PATHOPHYSIOLOGY



BNP = B-type (formerly brain) natruretic peptide
NI = Neprilysin inhibitor

ACE = angiotensin converting enzyme
ARB = angiotensin receptor blocker

LANDMARK CLINICAL TRIALS

- **PARAMOUNT (2012)**
  - NYHA Class II-III with *preserved* ejection fraction (EF>45%)
  - Randomized, double-blind study of 301 subjects
    - Goal doses: LCZ696 = 200 mg BID vs valsartan 160 mg BID
  - NT-proBNP was lower (p=0.005) in LCZ696 group at 12 weeks
    - Not statistically significant at 36 weeks
- **PARADIGM-HF (2014)**
  - NYHA Class II-IV with reduced ejection fraction (EF<40%)
  - Randomized, double-blind study of 8442 subjects
    - Goal doses: LCZ696 = 200 mg BID vs enalapril 10 mg BID
  - Primary outcome = composite of CV death or HF hospitalization
    - Significantly lower in LCZ696 group (HR = 0.8, p<0.001)
  - Trial was stopped early (27 months) due to overwhelming benefit

GUIDELINES

- ARNI = Angiotensin receptor/neprilysin inhibitor
- **ACC/AHA/HFSA Updated HF Guidelines (2016)**
  - Benefits (Level I, class B-R)
    - **Symptomatic HFrEF** (NYHA class II-III) able to tolerate ACEI/ARB
    - Replacement by an ARNI is recommended to reduce morbidity/mortality
  - Harms (Level III, B-R)
    - ARNI should not be given within 36 hours of an ACEI
    - ARNI should not be given to patients with a history of angioedema**
  - Caveats
    - Recommendations involving ARNIs are evidence level B-R
      - Based on only **one** high-quality randomized trial
    - Adverse reactions: hypotension, renal insufficiency, angioedema

**Based on increased risk of angioedema in clinical trials with omapatrilat, another ANRI

DOSING

- **How supplied**
  - Entresto® 24/26 mg (sacubitril 24 mg / valsartan 26 mg)
  - Entresto® 49/51 mg
  - Entresto® 97/103 mg

- **Recommended Dosing**
  - Starting dose: sacubitril/valsartan 49/51 mg twice daily
  - Titrate every 2-4 weeks to target dose of 97/103 mg twice daily
- **Dosing Adjustments**
  - Hepatic
    - Child-Pugh B: Reduce starting dose to 24/26 mg twice daily
    - Child-Pugh C: Use not recommended
  - Renal
    - eGFR <30 mL/min: Reduce starting dose to 24/26 mg twice daily

SAFETY

- **Phase I studies**
  - Minimal QT prolongation
  - No substantial CYP450 enzyme interactions
- **Phase II/III Trials**
  - PARAMOUNT
    - Similar rates of adverse events between LCZ696 and valsartan
    - Most common ADRs: hypotension, hyperkalemia, renal dysfunction
  - PARADIGM-HF
    - ADRs possibly lower than expected in practice, due to run-in period

Adverse event (%)	LCZ696 N=4187	Enalapril N=4212	P-value
Hypotension	17	12	<0.001
Hyperkalemia	12	14	0.007 (K+ >6 mg/dL)
Cough	9	13	<0.001
Dizziness/orthostasis	6	5	NS
Renal Failure	5	5	NS
Elevated SCr	5	6	0.007 (SCr ≥ 2.5)
Angioedema	0.45	0.24	NS

WARNINGS

- **Contraindications**
  - History of angioedema to ACEI/ARB
  - Concurrent ACE inhibitors
    - Avoid within 36 hours of switching to/from an ACEI
  - Concurrent aliskiren in patients with diabetes
- **Pregnancy and Lactation**
  - Sacubitril/valsartan is not recommended in pregnancy
    - FDA: "When pregnancy is detected, consider alternative drug treatment and discontinue as soon as possible…"
    - Valsartan: pregnancy category D
  - Avoid breastfeeding while taking sacubitril/valsartan
    - FDA: "…no information regarding the presence of sacubitril/valsartan in human milk"

OTHER CONSIDERATIONS

- **Administration**
  - Taken without regard to food
  - Tablets may be crushed
  - No oral liquid or IV formulation available
- **Monitoring**
  - Serum creatinine – baseline and periodic
  - Serum potassium – baseline and periodic
  - Blood pressure – routine, no less than 1-2 weeks after initiation

COST (30 DAY SUPPLY)

Drug	Qty	Cost*	Cost/unit
Sacubitril/valsartan 24-26 mg	60	$485.56	$8.09
Sacubitril/valsartan 49-51 mg	60	$485.56	$8.09
Sacubitril/valsartan 97-103 mg	60	$485.56	$8.09
Valsartan 80 mg			
Brand (Diovan®)	60	$489.60	$8.16
Generic	60	$278.63	$4.64
Enalapril 5 mg			
Brand (Vasotec®)	60	$1,157.12	$19.29
Generic	60	$111.08	$1.85
Lisinopril 10 mg			
Generic	30	$29.82	$0.99

* Based on average wholesale price (AWP). AWP data provided by Lexi-Comp

COUNSELING POINTS/ SUMMARY

- **Sacubitril/valsartan is a new drug for heart failure**
  - Decreases the risk of cardiovascular death and HF hospitalization
  - May also help treat blood pressure (in patients with hypertension)
- **Administration**
  - Twice daily
  - Take with/without food
  - Dose will be titrated in 2-4 weeks, if tolerated
- **Monitoring**
  - Blood pressure (daily, if possible)
  - Lab tests – SCr, K+ (periodic)
- **Interactions**
  - ACE inhibitors, aliskiren
- **Significant side effects**
  - Angioedema
  - Impaired/Worsening Renal Function
  - Hypotension
  - Hyperkalemia

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