Sacubitril/valsartan: A New Management Strategy for the Treatment of Heart Failure

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Disclosure

- Elizabeth Pogge reports no actual or potential conflicts of interest associated with this presentation
Learning Objectives

- Upon successful completion of this activity, pharmacists should be able to:
  - Explain why neprilysin inhibition is a target for the treatment of chronic heart failure
  - Describe key clinical trial aspects of the PARADIGM-HF study
  - Apply clinical trial data from PARADIGM-HF to a patient case with emphasis on appropriate patient selection, monitoring, and follow-up for sucubitril/valsartan
Chronic Heart Failure

- Worldwide heart failure incidence
  - 23 million

- Current standard of care (to target doses)
  - ACE inhibitors/ARBs
  - Beta blockers
  - Mineralocorticoid receptor antagonists

- Newly FDA approved therapies in 2015
  - Entresto® (sacubitril/valstartan)
  - Corlenor® (ivabradine)

Kitai T and Tang WW. *F1000Research* 2015, 4(F1000 Faculty Rev):1475
Mechanism of Action

Sacubitril

- Sabubitril is converted to an active formulation sacubitrilat by de-ethylation
  - The sacubitrilat inhibits the enzyme neprilysin
  - Neprilysin is responsible for the degradation of ANP, BNP, CNP and other vasoactive substances
  - These vasoactive substances help lower blood pressure and reduce blood volume
- Note: BNP levels are simple, objective measures of cardiac function used to monitor pts with HF
  - BNP levels will be acutely elevated in patients taking sabubitril
- NT-proBNP is not a substrate for neprilysin
  - NT-proBNP can be used in place of BNP

Key Clinical Trials

• PARADIGM-HF
  • 8,399 patients with NYHA class II-IV HF and an LVEF ≤ 40%
    • 70% of patients had NYHA class II HF
    • Average age: 63.8 yrs (79% male)
  • Double-blind trial comparing sacubitril/valsartan to enalapril
  • Stopped early at 27 months due to overwhelming benefit of sacubitril/valsartan

• Results:
  • Primary endpoint: Composite of CV mortality and first HF hospitalization

Study design in the PARADIGM-HF Trial

Single-blind run-in period
6-8 weeks

- Enalapril 10 mg twice daily
  - Median enalapril exposure: 15 days

- Entresto® 46/51 mg twice daily
  - Median Entresto® exposure: 29 days

Double-blind period

- Entresto® 97/103 mg twice daily
  - (n=4209)

1:1 randomization

- Enalapril 10 mg twice daily
  - (n=4233)

Results

# Entresto® Dosing

<table>
<thead>
<tr>
<th></th>
<th>Pt receiving &gt;50% target dose of ACEi</th>
<th>Pt receiving ≤50% target dose of ACEi</th>
<th>Pt receiving &gt;50% target dose of ARB</th>
<th>Pt receiving ≤50% target dose of ARB</th>
<th>Pt receiving &lt;50% target dose of ARB</th>
<th>Start Entresto® 24/26 mg BID</th>
<th>After 2-4 wks, ↑dose to 49/51 mg BID</th>
<th>After 2-4 wks, ↑dose to target maintenance dose of 97/103 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>Stop ACEi at least 36 hours before starting Entresto®</td>
<td>Start Entresto® 24/26 mg BID</td>
<td>Discontinue ARB, Start Entresto® 49/51 mg BID at next dosing interval</td>
<td>Discontinue ARB, Start Entresto® 24/26 mg BID at next dosing interval</td>
<td>Start Entresto® 24/26 mg BID</td>
<td>After 2-4 wks, ↑dose to 49/51 mg BID</td>
<td>After 2-4 wks, ↑dose to target maintenance dose of 97/103 mg BID</td>
<td>After 2-4 wks, ↑dose to target maintenance dose of 97/103 mg BID</td>
</tr>
<tr>
<td>ARB</td>
<td>Discontinue ARB, Start Entresto® 49/51 mg BID at next dosing interval</td>
<td>Discontinue ARB, Start Entresto® 24/26 mg BID at next dosing interval</td>
<td>Discontinue ARB, Start Entresto® 49/51 mg BID at next dosing interval</td>
<td>Discontinue ARB, Start Entresto® 24/26 mg BID at next dosing interval</td>
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<td>Discontinue ARB, Start Entresto® 24/26 mg BID at next dosing interval</td>
<td>Discontinue ARB, Start Entresto® 24/26 mg BID at next dosing interval</td>
</tr>
<tr>
<td>No ACEi or ARB</td>
<td>Start Entresto® 24/26 mg BID</td>
<td>Start Entresto® 24/26 mg BID</td>
<td>Start Entresto® 24/26 mg BID</td>
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</tbody>
</table>

https://www.entrestohcp.com/sfc/servlet.shepherd/version/download/06812000001NqWHAA0
Case #1

- CE is a 78 y/o female who presents for sacubitril/valsartan consideration
- PMH: New onset HFrEF (EF~30-35%), grade 1 diastolic dysfunction, NYHA class I; HTN; HLD
- Labs: (1 week ago)
  - K = 5.3 mg/dL, Cr = 1.0 mg/dL, weight = 115 lbs, BP = 119/74 mmHg, HR= 57 BPM
- Medications:
  - Ibuprofen 200 mg; 1 tablet daily as needed
  - Metoprolol succinate 25 mg daily
  - Pravastatin 20 mg daily
  - Furosemide 40 mg daily
  - Aspirin 81 mg daily
Case #1 Question

- What patient specific factor(s) should be considered before starting sacubitril/valsartan in CE?
  a) Poor renal function
  b) High serum potassium
  c) Current use of ibuprofen
  d) B and C
Clinical Pearls

• Monitoring with sacubitril/valsartan
  • K, Scr, BP, pro-BNP

• Exclusion criteria per clinical trial parameters
  • K > 5.2 mmol/L
  • GFR < 30 mL/min (use MDRD equations)

• Discontinue medications that can worsen renal function
  • NSAIDS, lithium, ACE inhibitors, aliskiren
Case #1 Continue

- CE is a 78 y/o female who presents for sacubitril/valsartan consideration
- PMH: New onset HFrEF (EF~30-35%), grade 1 diastolic dysfunction, NYHA class I; HTN; HLD
- Labs: (repeated today)
  - K = 4.2 mg/dL, Cr = 1.2 mg/dL, weight = 115 lbs, BP = 110/62 mmHg, HR= 64 BPM
- Medications:
  - Acetaminophen 325mg; 2 tablets twice daily
  - Metoprolol succinate 25 mg daily
  - Pravastatin 20 mg daily
  - Furosemide 40 mg daily
  - Aspirin 81 mg daily
Case #1 Question #2

- What patients specific factor(s) make CE not an ideal candidate for sacubitril/valsartan?
  a) No prior use of ACE inhibitor or ARB therapy
  b) NYHA class 1 heart failure
  c) SBP = 110 mmHg
  d) A and B
Patient Characteristics in PARADIGM-HF

- HFrEF ($\leq 40\%$)
- Male (79%), Caucasian (66%), North America (~7%)
- NYHA Class II-IV HF
  - 70% of patients had NYHA class II HF
- Average age: 63.8 yrs

Patient Characteristics in PARADIGM-HF

- Exclusion criteria: SBP < 100 mmHg
  - Baseline SBP average was ~ 122 mmHg
- Baseline use of other evidence-based therapies:
  - Beta-blockers (94%), diuretics (82%) and MRA (58%)
- Incidence of hypotension:
  - Sacubitril/valsartan: 18%
  - Enalapril: 12%

Clinical Pearls

• Considerations when starting sacubitril/valsartan:
  • SBP ≥ 100 mmHg
  • Clinical stable NYHA Class II/III HF
  • Currently tolerating ACE inhibitor or ARB at ≥ 50% of the target dose
  • Baseline use of other evidence-based therapies when appropriate
    • Beta-blockers
    • MRA
Case #2

- JA is a 66 y/o male who presents for sacubitril/valsartan consideration
- PMH: HFrEF (EF~30%), NYHA class II; HTN; HLD; GERD
- Labs: (today)
  - K = 4.0 mg/dL, Cr = 1.2 mg/dL, weight = 172 lbs, BP = 134/84 mmHg, HR= 80 BPM
- Medications:
  - Carvedilol 25 mg twice daily
  - Valsartan/HCTZ 320/25 mg daily
  - Atorvastatin 40 mg daily
  - Potassium 20 mEq daily
  - Furosemide 40 mg daily
  - Aspirin 81 mg daily
Question #3

• Does JA need a “washout” period before starting sacubitril/valsartan?
  a) Yes
  b) No
Clinical Pearls

- Discontinue ACE inhibitors 36-48 hours prior to initiation of first dose of sacubitril/valsartan (washout)
- No need for washout with ARB/aliskiren therapy
- Patients should be educated to discontinue all ACE inhibitors/ARB therapy with sacubitril/valsartan
  - Can be a concern with automatic pharmacy refills and/or additional providers that the patient sees
Case #2 Continue

• JA is a 66 y/o male who presents for sacubitril/valsartan follow-up 4 weeks later
• PMH: HFrEF (EF~30%), NYHA class II; HTN; HLD; GERD
• Labs: (today)
  • K = 5.1 mg/dL, Cr = 1.3 mg/dL, weight = 172 lbs, BP = 92/68 mmHg, HR= 62 BPM
• Medications:
  • Carvedilol 25 mg twice daily
  • Sacubitril/valsartan 97/103 mg twice daily
  • Atorvastatin 40 mg daily
  • Potassium 20 mEq daily
  • Furosemide 40 mg daily
  • Aspirin 81 mg daily
What medication adjustment would be best to considered in JA?

a) Discontinue sacubitril/valsartan
b) Lower the sacubitril/valsartan dose
c) Discontinue potassium and furosemide
d) Lower the carvedilol dose
Clinical Pearls

• Potassium supplements may need to be adjusted or discontinued

• Target doses are important in mortality reducing agents for heart failure
  • Beta-blockers, sacubitril/valsartan

• Diuretic doses may need adjusted
  • Sacubitril has diuresis properties
Patient Selection

- Stable, NYHA Class II/III symptoms in clinic
- ACEI/ARB >50% target dose
- BB +/- MRA at stable dose
- SBP > 100 mmHg
- K < 5.2 mmol/L
- Stable GFR > 30 mL/min/1.73^2
- No history of angioedema or ARB intolerance

Transition

- Hold ACEI for at least 36 hours prior to starting sacubitril/valsartan
- Start sacubitril/valsartan at 49/51 mg twice daily

1-2 week follow-up

- SBP < 95 mmHg or symptomatic hypotension
- GFR fall >25%
- K > 5.4 mmol/L
- Angioedema
- If no and tolerating, increase dose to 97/103 mg twice daily

1-2 week follow-up

- SBP < 95 mmHg or symptomatic hypotension
- GFR fall >25%
- K > 5.4 mmol/L
- Angioedema

Lillyblad MP. Annals of Pharmacotherapy; 2015: 49(11); 1237-1251.
Questions

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