SACUBITRIL-VALSARTAN
A FIRST-LINE DRUG IN HEART FAILURE
IS IT COST-EFFECTIVE?
OBJECTIVES

- Describe basic pathophysiology of heart failure
- Summarize current HF treatment options
- Evaluate the clinical and economic value of Entresto® (sacubitril-valsalartan)
HEART FAILURE IN AMERICA

- 6.5 million
- 1-million hospital admissions annually
- 1 in 8 death certificates mention HF
- $30.7 billion annually
- 5-year mortality of 50%
Impaired heart pumping
Inadequate perfusion
Systolic heart failure (LVEF < 40, HFrEF)
  CAD and MI (ischemia)
Diastolic heart failure (LVEF > 40, HFpEF)
  HTN and ischemic heart disease (impaired relaxation)
# HF Classes and Staging

<table>
<thead>
<tr>
<th>NYHA</th>
<th>ACC/AHA</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>High risk of developing HF</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td>II-III</td>
<td>C</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>IV</td>
<td>D</td>
<td>End-stage HF</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA guideline for the management of heart failure. *Circulation*
SYSTOLIC DYSFUNCTION

- Muscle ↓
- Na⁺ & H₂O ↑
- Remodeling
- Ventricular
  - dilation
  - Stretching
  - Fibrosis

End organ failure
- Sudden Cardiac death
- Pump failure

Heart Failure

- Myocyte Death ↑
- Neuro-hormones ↑
- Aldosterone ↑
- Renin Angiotensin System ↑

NATRIURETIC PEPTIDES

Pressure/volume overload

Vasodilatation

BNP

Inhibition SAS

Natriuresis/diuresis

Inhibition RAAS

http://heart.bmj.com/content/92/6/843
# TREATMENT SUMMARY

## HFrEF

**NYHA CLASS**

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
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<td></td>
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<tr>
<td>II</td>
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</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
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</tr>
</tbody>
</table>

### ACEi/ARB

- Hemodynamically stable

### Beta Blockers

- If ever symptomatic
- Hemodynamically stable

### Aldosterone Antagonist

- Hospitalized or ↑ natriuretic peptides

**All have been shown to reduce mortality and morbidity**

2013 ACCF/AHA guideline for the management of heart failure. *Circulation*
TREATMENT - OTHERS

- Digoxin
- Hydralazine/Isosorbide
- Loop diuretics

2013 ACCF/AHA guideline for the management of heart failure. *Circulation*
Entresto®
(sacubitril/valsartan) tablets
24/28mg · 49/51mg · 97/103mg

VALSARTAN

SACUBITRIL

NEPRILYSIN INHIBITION

RAAS

NATRIURETIC PEPTIDE SYSTEM

• Sodium and water retention
• Vasoconstriction
• Hypertrophy
• Fibrosis

• Natriuresis/diuresis
• Aldosterone suppression
• Vasodilation
• Inhibition of fibrosis

https://www.entrestohcp.com/heart-failure-guidelines
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.
Angiotensin–Nepriylisin Inhibition versus Enalapril in Heart Failure

PARADIGM-HF TRIAL

- Patients (N = 8,442)
  - NYHA: II-IV
  - Ejection fraction ≤ 35% (HFrEF)

[Diagram showing double-blind period and randomization between Entresto and Enalapril]

https://www.entrestohcp.com/heart-failure-guidelines

## PARADIGM-HF TRIAL

<table>
<thead>
<tr>
<th></th>
<th>NNT</th>
<th>RR Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>32</td>
<td>20%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>36</td>
<td>21%</td>
</tr>
<tr>
<td>Composite</td>
<td>22</td>
<td>20%</td>
</tr>
</tbody>
</table>

**CONCLUSION:** Sacubitril-valsartan is superior to enalapril in reducing risk of CV death and hospitalization in NYHA II - IV

Medicare Population

- **Tier-2**
  - 90-day supply = $200

- **Tier-4**
  - 90-day supply = $400

(Selecthealth.org/Pharmacy) (http://www.entresto.com/)

Selecthealth

- **Tier-2**
  - Copay card (30-d free / 10$ co-pay)
COST-EFFECTIVENESS

- Analytic tool using costs & health outcomes
- Determine value of intervention
- Make coverage/treatment decisions before real-world data is available

Cohen et al., *Journal of the American College of Cardiology (JACC)*, 2008
QALY

(QUALITY-ADJUSTED-LIFE-YEAR)

- 0 = Death
- 1 = Perfect health
QUESTIONS?
Cost-Effectiveness of Sacubitril-Valsartan in Patients With Heart Failure With Reduced Ejection Fraction

Alexander T. Sandhu, MD, MS; Daniel A. Ollendorf, PhD; Richard H. Chapman, PhD; Steven D. Pearson, MD, MSc; and Paul A. Heidenreich, MD, MS

- Based off PARADIGM-HF
- Methods
  - Markov decision model
- Duration
  - Lifetime
- Funding
  - U.S. Department of Veterans Affairs
  - Institute for Clinical and Economic Review

Sandhu, et al., Annals of Internal Medicine, 2016
Cost
- Sacubitril/Valsartan - $380.21/month
- Lisinopril - $1.87/month (instead of enalapril)
- Losartan - $6.93/month
- Health care costs – based on CMS data

Thresholds
- < $50,000/QALY = Very cost effective
- < $100,000/QALY = Intermediate value

Societal perspective
- Inclusion of all health care costs regardless of payer

Utilities (quality of life measure)
- EuroQol-5D data (patient surveys)
ASSUMPTIONS

- Event probabilities
  - Lisinopril = Losartan
- Losartan has no intolerance or angioedema
- CV mortality ↑ with age
- Non CV mortality = in all treatments
- Sacubitril-valsartan is effective till death
OUTCOMES

- Primary Outcome
  - $/QALY

- Other outcomes
  - Survival
  - QALYs
  - Cost

- Sensitivity & Probabilistic Analysis
  - 10,000 simulations

Sandhu, et al., Annals of Internal Medicine, 2016
## RESULTS

### Primary Outcome

- Sacubitril-valsartan vs. lisinopril

<table>
<thead>
<tr>
<th>NYHA II-IV</th>
<th>Hospitalization</th>
<th>Survival</th>
<th>QALY</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>0.83</td>
<td>6.98</td>
<td>5.71</td>
<td>$131,581</td>
</tr>
<tr>
<td>Sacubitril-valsartan</td>
<td>0.75</td>
<td>7.67</td>
<td>6.33</td>
<td>$160,785</td>
</tr>
</tbody>
</table>

$/QALY

- $47,053

- NYHA II: $44,530
- NYHA III-IV: $58,194

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• AUTHOR CONCLUSION:
  • Sacubitril-valsartan provides reasonable value in reducing CV mortality and morbidity in NYHA class II to IV.

• MY CONCLUSION:
  • Agree with the authors.
  • May be more cost-effective in NYHA class II patients.
<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA subgroup analysis</td>
<td>Limited efficacy data</td>
</tr>
<tr>
<td>Findings robust in sensitivity analysis</td>
<td>Readmission rates/costs not modeled</td>
</tr>
<tr>
<td>Cheaper, more common comparator (lisinopril)</td>
<td>Transition between NYHA classes not modeled</td>
</tr>
<tr>
<td></td>
<td>Not truly societal perspective</td>
</tr>
</tbody>
</table>
QUESTIONS?
Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared With Enalapril for the Treatment of Heart Failure With Reduced Ejection Fraction

Jordan B. King, PharmD, a Rashmee U. Shah, MD, MS, b Adam P. Bress, PharmD, MS, a Richard E. Nelson, PhD, c,d Brandon K. Bellows, PharmD, MS a,e

Based off of PARADIGM-HF

Methods
  ▪ Markov Decision model

Duration
  ▪ Lifetime

King, et al. JACC: Heart Failure, 2016
King, et al. JACC: Heart Failure, 2016
Cost
- Sacubitril/Valsartan - $380/month
- Enalapril- $23/month

Thresholds
- < $50,000/QALY
- < $100,000/QALY

3rd party perspective
- Only direct costs

Utilities (quality of life measure)
- CARE-HF trial
ASSUMPTIONS

- Enalapril = Sacubitril-valsartan
  - Non-HF event probabilities/cost
  - Readmission rate
  - Disease progression
- Patients remained in treatment group through life
- CV mortality rates constant till death
- Sacubitril-valsartan effective till death
- Medication prices fixed over time

Sandhu, et al., Annals of Internal Medicine, 2016
OUTCOMES

- Primary Outcome
  - $/QALY

- Other outcomes
  - Survival
  - QALY
  - Cost

- Sensitivity Probabilistic Analysis
  - 10,000 simulations
RESULTS

- Primary Outcome
  - Sacubitril-valsartan vs. enalapril

<table>
<thead>
<tr>
<th>Survival (y)</th>
<th>QALY</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>8.4</td>
<td>5.83</td>
</tr>
<tr>
<td>Sacubitril-valsartan</td>
<td>9.5</td>
<td>6.59</td>
</tr>
</tbody>
</table>

$/QALY

$50,959

King, et al. JACC: Heart Failure, 2016
PROBABILISTIC SENSITIVITY

King, et al. JACC: Heart Failure, 2016
• AUTHOR CONCLUSION:
  • Sacubitril-valsartan has the potential to increase quality and quantity of life, and may be cost-effective.

• MY CONCLUSION:
  • Agree with the authors.
  • Sacubitril-valsartan provides reasonable value.
<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Robust sensitivity analysis</td>
<td>Limited efficacy data</td>
</tr>
<tr>
<td>Lifetime follow-up</td>
<td>3rd party perspective</td>
</tr>
<tr>
<td>Thorough model description</td>
<td>No funding description</td>
</tr>
<tr>
<td>NYHA transitions were modeled</td>
<td></td>
</tr>
</tbody>
</table>
QUESTIONS?
SUMMARY OF RESULTS

- Sandhu et. al (2016) = $47,053
- King et. al (2016) = $50,959
- Gaziano et. al (2016) = $45,017

- All modelled PARADIGM-HF data
Apixaban vs. warfarin in atrial fibrillation = $39,351

Pembrolizumab vs standards of care in NSCLC = $97,621
Sacubitril-valsartan provides reasonable value for treatment of SHF when compared to ACEi’s

Educate patients and providers on the potential benefits/costs

Recommend that SHF patients with NYHF stage II-III consider initiating sacubitril-valsartan
  ▪ Evaluate willingness-to-pay on patient to patient case
    ▪ Co-pay cards

Longer duration of treatment = more cost-effective

Long-term efficacy data needed!!!
FUTURE/ONGOING STUDIES OF SACUBITRIL-VALSARTAN

- Alzheimer’s
- Prevention of HF after MI
- HFpEF
- Exercise tolerance
- Pediatric HF
- Advanced HF

http://www.medicalnewstoday.com/articles/280574.php
THANK YOU

- **Topic mentor:**
  - Dr. Munger

- **Faculty Evaluators:**
  - Dr. Bellows
  - Dr. Crouch
QUESTIONS?
REFERENCES