HEART FAILURE: PHARMACOTHERAPY UPDATE

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OBJECTIVES

• At the conclusion of this presentation, audience members should be able to:
  • Define heart failure (HF) including possible causes as well as classification and staging
  • Summarize treatment options for HF with reduced ejection fraction (HFrEF)
  • Incorporate 2016 focused HF treatment update recommendations
  • Explain the mechanism of action, side effects, dosing, appropriate monitoring parameters
    and cost for sacubitril/valsartan and ivabradine
  • Identify pivotal trials for sacubitril-valsartan and ivabradine

HEART FAILURE REVIEW

5.1 million
x 1.25 = 6.375 million

HF Diagnosis

40 years old = 

DEFINING HEART FAILURE

• HFrEF
  • ≤ 40%
  • Systolic

• HFrEF
  • >40%
  • Diastolic
5 CAUSES OF HEART FAILURE

- Dilated cardiomyopathies (CM)
- Familial CM
- Endocrine & Metabolic
- Toxic CM
- Tachycardia-induced CM
- Peripartum CM
- Iron overload CM
- Amyloidosis/sarcoidosis
- Stress CM (Takotsubo)

6 HEART FAILURE CLASSIFICATION & STAGING

- NYHA Class
  - I: No limitations of physical activity
  - II: Ordinary activity results in symptoms
  - III: Less than ordinary activity causes symptoms
  - IV: Unable to do any activity w/o symptoms or symptoms at rest

- ACCF/AHA Stage
  - A: High risk but w/o heart disease or symptoms of HF
  - B: Structural heart disease but w/o signs/symptoms
  - C: Structural heart disease with prior or current symptoms
  - D: Refractory HF requiring specialized interventions

7 HEART FAILURE TREATMENT

- ACE/ARB
- Beta-blocker
- Aldosterone antagonist
- Diuretics
- Digoxin
- Sacubitril-Valsartan
- Ivabradine

8 HEART FAILURE TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduce Mortality</th>
<th>Reduce Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ARB</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Aldosterone Receptor Antagonist</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hydralazine-Isoxorbide Dinitrate*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Digoxin</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sacubitril-Valsartan</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

* African Americans
NEW AGENTS

- Sacubitril-Valsartan
  - Mechanism of Action (MOA)
  - PARADIGM Trial review
  - Side effects
  - Dosing
  - Monitoring parameters
  - Cost

- Ivabradine
  - Mechanism of Action
  - SHIFT Trial review
  - Side effects
  - Dosing
  - Monitoring parameters
  - Cost
PARADIGM TRIAL

- Study design
  - Double-blind
- Study participants
  - 8442
  - Class II, III, IV
  - LVEF ≤40% (35%)
- Exclusion criteria
  - Symptomatic hypotension
  - Significant renal dysfunction
  - Potassium >5.2 mmol/L
  - History of angioedema or intolerance to ACE/ARB

Outcomes
- Primary
  - Composite death from CV cause or first HF hospitalization
- Secondary
  - All-cause death
  - KCCQ score
  - Time to new onset atrial fibrillation
  - Decline in renal function

PARADIGM TRIAL

SACUBITRIL-VALSARTAN

- 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
- ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor
- ARNI should not be administered to patients with a history of angioedema
17 SACUBITRIL-VALSARTAN

- Side Effects
  - Hypotension
  - Cough
  - Angioedema
- Monitoring
  - Serum creatinine
  - Potassium
  - BP
- Dosing
  - 24/26 mg, 49/51 mg, 97/103 mg
  - Twice daily dosing
  - Must be off ACE inhibitor 36 hrs before initiating
- Cost
  - $400-500/month

19 MOA: IVABRADINE

$I_f$ channel blocker (Funny channel)

https://www.corlanorhcp.com/mechanism-of-action/

18

20 MOA: IVABRADINE

https://www.corlanorhcp.com/mechanism-of-action/
**SHIFT TRIAL**

**Study design**
- Randomized, double-blind, placebo-controlled, parallel-group

**Study participants**
- 6558
- Sinus rhythm, resting HR ≥70 BPM
- EF ≤35%
- Previous admission for HF in last 12 months

**Exclusion criteria**
- Recent MI (2 months)
- Ventricular or AV pacing >40%
- Atrial fibrillation or flutter
- Symptomatic hypotension

**Outcomes**
- **Primary**
  - Composite CV death or hospitalization for HF
- **Secondary**
  - Composite CV death or hospitalization for HF
  - Receiving at least 50% target BB dose
  - All-cause death
  - CV death
  - Hospitalization for HF and all-cause hospitalization

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Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

**Summary**
Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart rate reduction by the selective ion channel inhibitors on outcomes in heart failure.

**Methods**
Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus clothes with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β-blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine started to a maximum dose of 7.5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospitalization for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN04999860.

Figure 2: Mean heart rate during the study in the initial study population, by allocation group.
SHIFT TRIAL

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Ivabradine group (n=2482)</th>
<th>Placebo group (n=2464)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>99 (4.0%)</td>
<td>107 (4.3%)</td>
<td>0.82 (0.75-0.89)</td>
</tr>
<tr>
<td>Mortality endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>90 (3.6%)</td>
<td>99 (4.0%)</td>
<td>0.90 (0.80-1.02)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>41 (1.6%)</td>
<td>48 (1.9%)</td>
<td>0.96 (0.89-1.03)</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>62 (2.5%)</td>
<td>81 (3.3%)</td>
<td>0.76 (0.65-0.90)</td>
</tr>
</tbody>
</table>

Other endpoints

| All-cause hospital admission | 132 (5.4%) | 135 (5.5%) | 0.90 (0.83-0.97) | 0.043 |
| Hospital admission for worsening heart failure | 134 (5.6%) | 172 (7.0%) | 0.74 (0.64-0.86) | <0.0001 |
| Arousal cardiovascular hospital admission | 97 (3.9%) | 115 (4.6%) | 0.86 (0.75-0.99) | 0.0003 |
| Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-suicidal suicide attempt | 83 (3.4%) | 97 (4.0%) | 0.82 (0.74-0.90) | <0.0001 |

Data are number of faces events (%), hazard ratio (95% CI), p values.

Table 3: Effects of primary and major secondary endpoints

IVABRADINE

- Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF (LVEF ≤ 35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.

Side Effects
- Bradycardia
- Hypertension
- Atrial fibrillation
- Phosphenes

Monitoring
- Heart rate
- Blood pressure
- Cardiac rhythm

Dosing
- 5 mg, 7.5 mg
- Twice daily dosing

Cost
- $485/month
PATIENT CASE

JR 64 yo Male

PMH
- STEMI 2009
- Ischemic CM (EF 30%), NYHA Class II
- DM 2
- Afib

Labs
- SCr 1.12, K 4, A1c 6.9, INR 2.7, Hgb 14

Vitals
- BP 110/76, P 85, RR 12

PE
- Large CTA, trace bilateral edema, JVP WL

Medications
- Carvedilol 25 mg BID
- Lisinopril 20 mg daily
- Spironolactone 12.5 mg daily
- Furosemide 40 mg BID
- Metformin 1000 mg BID
- Atorvastatin 40 mg nightly
- Warfarin 40 mg nightly
- Aspirin 81 mg daily

REFERENCES


6. Sacubitril and valsartan: Drug information. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 26, 2017.)

7. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective L current inhibition with ivabradine. Drugs 2004; 64 (16): 1757-1765


9. Inducible Drug Information. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 26, 2017.)