Objectives

- Briefly describe HF clinical syndrome and definitions
- Review HFrEF medication therapy
- Review Updated HF Guideline recommendations
- Review supportive data for key recommendations
- Briefly review drugs that can exacerbate HF
Heart Failure – A clinical syndrome

- Typical symptoms that may be accompanied by signs
- ...caused by a structural and/or functional cardiac abnormality
- ...resulting in reduced CO and/or elevated intracardiac pressures at rest or during stress
- Pt can present with asx structural or functional cardiac abnormalities (systolic or diastolic LV dysfunction)
- Important to start tx early

Heart Failure- Classification

- Stage A- At risk
- Stage B- Structural damage without Sx
- Stage C- Structural damage with Sx
- Stage D- End-stage
- NYHA Class I- no limitation
- NYHA Class II- limitation with ordinary activity
- NYHA Class III- limitation with less than ordinary activity
- NYHA Class IV- Sx at rest/end-stage
Classification of Recommendations and Levels of Evidence

Key Updates

- Biomarkers
- Pharmacotherapy
  - HFrEF
  - HFP EF
- Nutritional Supplements
- Anemia
- HTN (New section!)
- Sleep Disorders
Biomarkers

- Well established role for
  - Assist in Dx or exclusion of HF as a cause of sx in chronic HF (ambulatory) or ADHF

- Role in population screening is emerging
  - Low diagnostic sensitivity in obese
  - Baseline levels useful in admissions

Pharmacological Treatment for Stage C HHrEF

ANGIOTENSIN-NEPRILYSIN INHIBITOR
Pharmacological Treatment for Stage C HF With Reduced EF

Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF/EF to reduce morbidity and mortality.</td>
<td>NEW: New clinical trial data prompted clarification and important updates.</td>
</tr>
</tbody>
</table>

ARNI

- Angiotensin Receptor-Nephrilysin Inhibitor
- Sacubitril-Valsartan
- MOA- Promote natriuretic response
ARNI- Mechanism of Action


PARADIGM-HF

- RCT
- N= 8442
- EF 40% or less, NYHA Class II-IV
- Enalapril 10 mg BID v. Sacubitril-valsartan 200 mg BID
  - Controversy; Data supports this dose
  - Average dose: 18.9 mg/day (CONSENSUS= 16.6)
PARADIGM-HF Study Design

**SINGLE-BLIND RUN-IN PERIOD**
(6 to 8 weeks)

- **Primary Endpoint**
  - Composite of death from CV causes OR a 1st hospitalization for HF

- **Secondary Endpoints:**
  - Time to death from any cause
  - Change from BL to 8 months in clinical summary score
  - Time to N.O. Afib
  - Time to 1st occurrence of a decline in renal function (ESRD or dec in eGFR 50% or more than 30ml/min).

**DOUBLE-BLIND PERIOD**
(duration was event-driven; median follow-up duration was 27 months)

- **Entresto**
  - 97/103 mg twice daily
  - N=4209

- **Enalapril**
  - 10 mg twice daily
  - N=4235

PARADIGM-HF - Results

- BB (93%), Diuretic (80%), MRA (54-57%)
- 20% decrease in mortality (HR 0.80; CI 0.73 to 0.87; P<0.001)
- (SOLVD trial we have a 16% dec in mortality) (N= 2569, dec 16% in mortality)
- NNT = 21 (death from CV cause or hospitalization)
- NNT = 32 (death from CV causes)

Guideline Directed Medical Therapy

<table>
<thead>
<tr>
<th>Benefit Demonstrated in RCTs</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

*Circulation. 2013;128:e240-e327*
Pointers

- Dose- 50 mg BID up to 200 mg BID
- Dosage forms: tablet 24/26 mg, 49/51 mg, 97/103 mg
- Valsartan in Entresto is more bioavailable than other marketed tablet formulations
- Entresto 24/(26) mg = valsartan 40 mg
- Entresto 49/(51) mg = valsartan 80 mg
- Entresto 97/(103) mg = valsartan 160 mg

ACE CONVERSION CHART

<table>
<thead>
<tr>
<th>LISISNPRIL</th>
<th>ENALAPRIL</th>
<th>SACUBITRIL-VALSARTAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>20-40</td>
<td>20-40</td>
<td>200</td>
</tr>
</tbody>
</table>
# ACE CONVERSION CHART

<table>
<thead>
<tr>
<th>LISINOPRIL</th>
<th>ENALAPRIL</th>
<th>SACUBITRIL-VALSARTAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/day</td>
<td>5 mg/day</td>
<td>50 mg BID</td>
</tr>
<tr>
<td>10 mg/day</td>
<td>100 mg/day</td>
<td>100 mg BID</td>
</tr>
<tr>
<td>20-40 mg/day</td>
<td>20-40 mg/day</td>
<td>200 mg BID</td>
</tr>
</tbody>
</table>

# ARB CONVERSION CHART

<table>
<thead>
<tr>
<th>LOSARTAN</th>
<th>VALSARTAN</th>
<th>SACUBITRIL-VALSARTAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day</td>
<td>40 mg BID</td>
<td>50 mg BID</td>
</tr>
<tr>
<td>50 mg/day</td>
<td>80 mg BID</td>
<td>100 mg BID</td>
</tr>
<tr>
<td>100-150 mg/day</td>
<td>160 mg BID</td>
<td>200 mg BID</td>
</tr>
</tbody>
</table>
### Pharmacological Treatment for Stage C HFrEF

**IVABRADINE**

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**Table 3. Drugs Commonly Used for HFrEF (Stage C HF)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>122.7 mg QD</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10–20 mg BID</td>
<td>16.6 mg QD</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5–10 mg QD</td>
<td>40 mg QD</td>
<td>N/A</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg QD</td>
<td>20–40 mg QD</td>
<td>32.5–35.0 mg QD</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg QD</td>
<td>8–16 mg QD</td>
<td>N/A</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td>N/A</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg QD</td>
<td>10 mg QD</td>
<td>N/A</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg QD</td>
<td>4 mg QD</td>
<td>N/A</td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4–8 mg QD</td>
<td>32 mg QD</td>
<td>24 mg QD</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg QD</td>
<td>50–150 mg QD</td>
<td>129 mg QD</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20–40 mg BID</td>
<td>160 mg BID</td>
<td>254 mg QD</td>
</tr>
<tr>
<td>ARNI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/Valsrartan</td>
<td>49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)</td>
<td>97/103 mg BID (sacubitril/valsartan)</td>
<td>375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID</td>
</tr>
</tbody>
</table>
## Pharmacological Treatment for Stage C HF With Reduced EF

### Ivabradine

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, 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.</td>
<td>NEW: New clinical trial data.</td>
</tr>
</tbody>
</table>

### Ivabradine

- MOA: Inhibits If current in SA node to reduce HR
- Indication: reduce risk of hospitalization for worsening HF in:
  - Pts with stable, Sx HFrEF (EF ≤35%)
  - Who are in SR with resting HR ≥70 bpm
  - Who are on maximally tolerated BB tx or have a Cl to BB tx
SHIFT Trial


- RCT, DB

- N= 6558

- EF 35% or lower, Sx HF, SR with HR >/= 70 bpm, admission for HF w/in previous year, and on stable background tx including BB (if tolerated)

- Median f/u 22.9 months
SHIFT- Trial Design

SHIFT- Results

- Primary endpoint - Composite of cardiovascular death or hospital admission for worsening heart failure
  - Decreased by 18%
- 26% decrease in admissions for worsening HF
Pharmacological Treatment for Stage C HF With Reduced EF

IRON DEFICIENCY

Iron Deficiency and HFrEF

<table>
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</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients with NYHA class II and III HF and iron deficiency (ferritin &lt;100 ng/mL or 100 to 300 ng/mL if transferrin saturation is &lt;20%), intravenous iron replacement might be reasonable to improve functional status and QoL.</td>
<td>NEW: New evidence consistent with therapeutic benefit.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.</td>
<td>NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.</td>
</tr>
</tbody>
</table>
IRON DEFICIENCY AND HFrEF

ID in HFrEF Data

- **FAIR-HF**
- **Subanalysis of FAIR-HF**
  - Treatment of ID with FCM in HF is equally efficacious irrespective of anemia.
  - Fe status should be assessed in Sx HF both with and w/o anemia and tx of ID should be considered.
- **COHNFIRM-HF**
  - Multi-center DB, PCT. N= 304. EF <= 45%, elevated natriuretic peptides and ID.
  - Treatment of Sx, ID HF patients with FCM over a 1yr period resulted in sustainable improvement in functional capacity, sx, and QoL and
  - May be associated with risk reduction of hospitalization for worsening HF
Pharmacological Treatment for Stage C HFpEF

MINERALOCORTICOID RECEPTOR ANTAGONISTS

<table>
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<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate &gt;30 mL/min, creatinine &lt;2.5 mg/dL, potassium &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.</td>
<td>NEW: Current recommendation reflects new RCT data.</td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
<td>The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>
TOPCAT-HF

- RCT, DB
- N=3445
- HFpEF EF ≥ 45%
- MRA (spironolactone) v. PLCB
- 1° endpoint- Composite death from CV causes, aborted CV arrest, or hospitalization for the management of HF.
- Mean f/u 3.3 years
- Clinically significant reduction in incidence of hospitalization only

TOPCAT-HF, cont.

- ADE- hyperkaleemia, increased SrCr
- With frequent monitoring, there was no significant differences in the incidence of serious ADE, SrCr > 3 mg/dl, or HD.
Pharmacological Treatment for Stage C HFpEF

<table>
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<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.</td>
<td>NEW: Current recommendation reflects new data from RCTs.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C</td>
<td>Routine use of nutritional supplements is not recommended for patients with HFpEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>

Prevention Strategies

TREATING HTN TO REDUCE THE INCIDENCE OF HF
HYPERTENSION

Treating Hypertension to Reduce the Incidence of HF

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.</td>
<td>NEW: Recommendation reflects new RCT data.</td>
</tr>
</tbody>
</table>

Prevention Strategies

DRUGS THAT MAY CAUSE OR EXACERBATE HEART FAILURE
Drugs that can exacerbate HF

- Drugs may cause or exacerbate HF by:
  - Causing direct myocardial toxicity;
  - Negative inotropic, lusitropic, or chronotropic effects;
  - Exacerbating hypertension;
  - Delivering a high sodium load; or
  - Drug-drug interactions (DDI) that limit the beneficial effects of HF medications

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Drugs that can exacerbate HF

  - Polypharmacy = LT use of ≥5 medications
  - Pts ≥ 2 medications had a 13% risk of an adverse DDI
  - Pts ≥ 4 medications → 38%
  - Pts ≥7 medications 82%
  - Prevention of DDIs → ↓ admissions → ↓ costs & QoL
Potassium Binders

IMPROVING ADHERENCE TO GDMT FOR HFREF WITH POTASSIUM BINDERS

Potassium Binders

- Hyperkalemia (HK) incidence higher in HF, CKD
- Drug-induced HK most commonly associated with RAAS inhibitors
- Typical management includes loop diuretics, close monitoring, discontinuation of beneficial agent → undesirable outcomes
- Sodium polystyrene sulfonate (SPS/Kayexalate) only option for decades
- High sodium content, GI ADEs, lack clinical data
Potassium Binders- Patiromer

- Patiromer sobitex calcium (patiromer)- Veltassa (Approved 2015)
- Non-absorbed oral K+-binding polymer.
- Acts primarily in distal colon (where the K+ is the highest), to increase fecal excretion (preferentially exchanges K+ for H/Na.
- Not specific for K+ (hypomagnesemia)
- OPAL-HK, AMETHYST-DN, PEARL-HF
- Dose: 8.4g q daily, Increase by increments of 8.4g q 1 week intervals to max 25.2g/d
- ADEs: HypoMg++, HypoK+ (5%), constipation, diarrhea, flatulence, nausea
- Oral medications should be administered at least 3 hours before or 3 hours after patiromer

Potassium Binders- ZS9

- Sodium zirconium cyclosilicate (ZS9)- Lokelma (Approved 2018)
- Inorganic, unabsorbable polymer of zirconium silicate
- 10X specific for potassium as patiromer
- 400 mg Na++ per 5 g dose
- HARMONIZE, Substudy in HF
- Dose: 10 g TID initially x up to 48h; chronic 5-15 g/day. Increase in 5g at 1 week intervals.
- ADEs- edema, peripheral edema, hypoK (4%)
- In general, other oral medications should be administered at least 2 hours before or 2 hours after ZS9
WRAP UP....

• https://youtu.be/aS3xaXsh6vo

References

References, cont.


QUESTIONS?

WHEN YOU TELL THE INTERN TO TAKE A BIG WIFF OF THE ACETYLCYSTEINE