Medications in the management of patients with Heart Failure with reduced Ejection Fraction (HF rEF)

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Disclosure
• Speaker for Novartis Pharmaceuticals

Discussion
• Guideline-based pharmacotherapy
  ➢ 2013 ACCF-AHA HF Medication Guideline
• New medications, recently approved for the treatment of patients with HFrEF
• Common medications used for Inotropic support
Epidemiology

- 5.7 million people in the United States with HF
- 1.1 million ADHF hospitalizations each year
  - Leading cause hospital admission: pts > 65 years
  - National average 30 day readmission rate 23%
  - Mortality 50% at 5 years
  - Cost $32 billion/year
    - More costly than all forms of cancer combined

Heart failure is a clinical diagnosis

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopnea/PND</td>
<td>Ankle edema</td>
</tr>
<tr>
<td>Neck vein distention</td>
<td>Night cough</td>
</tr>
<tr>
<td>Rales</td>
<td>Exertional dyspnea</td>
</tr>
<tr>
<td>Cardomegaly</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Acute pulm edema</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>JVD &gt; 5 cm H2O</td>
<td>Tachycardia (&gt;120)</td>
</tr>
<tr>
<td>53 gallop</td>
<td>Decreased VC</td>
</tr>
<tr>
<td>HF</td>
<td></td>
</tr>
<tr>
<td>Circulation time &gt; 25 sec</td>
<td></td>
</tr>
<tr>
<td>* Weight loss on HF tx</td>
<td></td>
</tr>
</tbody>
</table>

CHF = 2 major or 1 major + 2 minors

Framingham criteria


Stages, Phenotypes and Treatment of HF
Heart Failure Therapeutic Goal

• Primary goal = Reduce mortality
  – Prevent progression to symptoms
  – Prevent progressive LV dysfunction
  – Alleviate or reduce symptoms
  – Slow disease progression
  – Improve quality of life (QOL)
  – Reduce hospitalizations
  – Prevent sudden death

• Stage D: heart transplant, permanent mechanical support, chronic inotropic support (palliative care), compassionate end-of-life care, hospice

Neurohormonal Blockade has had a significant impact on heart failure survival since 1990

ACE INHIBITORS
Renin-Angiotensin-Aldosterone Pathways

SOLVD Treatment trial

SOLVD Prevention: Lower EF → Greater Benefit
ACEIs in CHF: A Pooled Analysis of 32 Randomized Trials

Garg et al. JAMA. 1995; 273:1450

ACEI and Renal Function
- Benefit even if Creatinine rises

Testani JM, et al. Circ HF 2011

ACE Inhibitors in Heart Failure
- Improve symptoms, clinical status, and exercise capacity
- Improves cardiac function
- Reduces hospitalizations
- Attenuates LV remodeling
- Prolongs survival
- Reduces vascular events
ACC/AHA classifications of Class and Level of Evidence

- **Class I:** Conditions for which there is evidence and/or general agreement that this medication is useful and effective.
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the medication.
- **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.
- **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is evidence and/or general agreement the medication is not useful/effective and in some cases may be harmful.

**ACE Inhibitors: Guideline-Based Recommendations**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Baseline administration to symptomatic and asymptomatic patients with LVEF ≤ 40% to reduce morbidity and mortality, unless contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>ACE inhibitors should be titrated to doses used in clinical trials as tolerated during concomitant up-titration of BB</td>
</tr>
<tr>
<td>Intolerance</td>
<td>Due to cough: substitute ARBs. Due to hyperkalemia or renal insufficiency: Consider hydralazine/nitrate combination. Due to angioedema: consider ARB. * Angioedema is infrequently reported with ARBs.</td>
</tr>
</tbody>
</table>

**Angiotensin Receptor/Neprilsin Inhibition**

- Neprilysin inhibitor: ARB: Sacubutril/Valsartan
  - Neprilysin degrades vasoactive peptides, breakdown and Angiotensin-II
  - Neprilysin inhibition prevents the degradation of these vasoactive peptides and increases their biologic activity
- Sacubutril-mediated Neprilysin inhibition prevents degradation of vasoactive peptides and increases levels of the peptides
- Angiotensin receptor inhibition via Valsartan blocks the effects of Ang by Angiotensin II type 1 receptors
- Dose: 24/26 mg, 48/51 mg, 72/76 mg twice daily
- Potential adverse effects: cough, hyperkalemia, renal dysfunction, angioedema, and hypotension
PARADIGM-HF: Effect of ARNi versus Enalapril on Primary Endpoint and its Components

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LCB886 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>914 (21.6%)</td>
<td>1117 (26.3%)</td>
<td>0.80 (0.73–0.87)</td>
<td>0.000002</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>506 (12.3%)</td>
<td>693 (16.3%)</td>
<td>0.80 (0.71–0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>637 (15.8%)</td>
<td>656 (15.6%)</td>
<td>0.79 (0.71–0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

McMurray, J et al. NEJM 2014; 371:

ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

ARBs:
Guideline-Based Recommendations

- ACC/AHA recommendations
  - Alternative when ACEI not tolerated (Class I)
  - Added to an ACEI (Class IIb)
  - Added to an ACEI before β blockers (Class III)
  - ACEI, ARB, and aldo blocker NOT recommended (Class III)
- Alternative to ACEI
  - ACEI should be tried first
  - Caution with angioedema
- Persistent hypertension or symptoms
  - Use optimal doses of ACEI and β blockers first
BETA BLOCKERS

How do Beta Blockers improve Heart Failure?

- Upregulation of beta receptors
- Improved coupling of beta receptors to secondary intracellular signals
- Alterations in myocardial metabolism
- Improved calcium transport
- Inhibition of the renin-angiotensin system
- Inhibition of endothelin and cytokine release

Effect of Beta Blockade on Outcome in Patients with HF and Post-MI LVD
Clinical Pharmacology of Beta-Adrenergic Antagonist

<table>
<thead>
<tr>
<th>BB</th>
<th>B1/B2 Receptor Selectivity</th>
<th>Vasodilator Mechanism</th>
<th>Lipid Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>75</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>7</td>
<td>Alpha 1 antagonist</td>
<td>++</td>
</tr>
</tbody>
</table>

Carvedilol vs Metoprolol Succinate

<table>
<thead>
<tr>
<th>Advantage</th>
<th>CARVEDILOL</th>
<th>METOPROLOL SUCCINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>Low-dose responsiveness</td>
<td>Once daily dosing</td>
</tr>
<tr>
<td>Vasodilator effect</td>
<td>Treating concomitant hypertension, initiating HF treatment, where BP not a limitation</td>
<td>Patients with marginal BP, less light-headedness</td>
</tr>
<tr>
<td>Spec Populations</td>
<td>Diabetes, less insulin resistance, less new-onset DM</td>
<td>Less potential for bronchospasm</td>
</tr>
</tbody>
</table>

Important facts on Beta blocker therapy

Why start BB therapy in the hospital?
- IMPACT-HF Primary Endpoint: Patients who received BBs had improved survival at 6 months

Does Baseline Heart Rate matter?

Gatto WA et al. JACC 2004; 43: 1534-41

Lechat et al. Circ 2001; 103: 1103-8
## Beta Blockers: Guideline-Based Recommendations

### General
- Recommended for symptomatic and asymptomatic patients with reduced LVEF (≤ 40%) to reduce M&M
- Use drugs shown to be effective in clinical trials
- Initiating after optimizing volume status and discontinuation of IV inotropic agents
- In the presence of volume overload, do not administer without a concomitant diuretic
- Whenever possible, initiate prior to hospital discharge in stable patients

### Following Decompensation
- Initiate at a low dose
- Up-titrate gradually, generally ≥ 2 weeks intervals to target doses shown to be effective in clinical trials
- Target dose in 8-12 weeks
- Maintain at maximum tolerated dose

### Initiation, Dosing
- Initiate at a low dose
- Up-titrate gradually, generally ≥ 2 weeks intervals to target doses shown to be effective in clinical trials
- Target dose in 8-12 weeks
- Maintain at maximum tolerated dose

### If symptoms worsen or side effects appear
- Adjust dose of diuretic and/or other vasoactive medication

### If up-titration continues to be difficult
- Prolong titration interval
- Reduce target dose
- Consider referral to a HF specialist

### Acute exacerbation of Chronic HF
- Maintain therapy
- Reduce dose if possible
- Avoid abrupt disruption
- If discontinued/reduced, reinstate gradually before discharge

### Concomitant Disease
- Use in the majority of patients even with DM, COPD or PVD
- Consider in pts with reactive airway disease or symptomatic bradycardia
- Caution in pts with DM and recurrent hypoglycemia; symptomatic bradycardia/hypotension
- Avoid in pts with severe bronchospasm

### ALDOSTERONE ANTAGONIST
Aldosterone in Heart Failure

- Increased by > 20X in Heart Failure
- Released from adrenal cortex and other tissues in response to Ag II, ACTH and potassium
- Promotes Na retention; K and Mg wasting
- Induces myocardial vascular fibrosis
- Activates the sympathetic NS and inhibits the Parasympathetic NS
- Aldosterone “escape” from ACE inhibition

Mechanism of Action

- Aldosterone antagonists: receptor antagonist at the mineralocorticoid receptor.
- Antagonism of these receptors inhibits sodium resorption in the collecting duct of the nephron in the kidneys.
- This interferes with sodium/potassium exchange, reducing urinary potassium excretion and weakly increasing water excretion (diuresis).
- In CHF, used in addition to other drugs for additive diuretic effect, which reduces edema and cardiac workload.

Randomized Aldactone Evaluation Study (RALES)

- 1,663 pts:
  - 70% NYHA Class III; 30% Class IV
  - Exclusion: Cr > 2.5, K > 5
  - Spironolactone 25mg qd
  - Laboratory measurements at 1 and q 4 wks
  - Drug held for K > 6 or Cr > 4

*Randomized Aldactone Evaluation Investigators*  
*N Engl J Med 1999; 341:709-717*
**EPHESUS**

Eplerenone for LV dysfunction after MI

- Selective aldosterone blocker in 3,313 pts
- Post MI d3-14, EF <40% and CHF (if no DM)
- Exclusion criteria: cr >2, K > 5
- Addition of eplerenone to OMT reduces morbidity and mortality among patients with acute myocardial infarction complicated with ventricular dysfunction and heart failure.

Pitt, B et al. NEJM 2003; 348:1309-1321

**EMPHASIS-HF: Eplerenone effects in NYHA Class II pts with LVEF ≤ 35%**

- 2, 737 pts
- All NYHA Class II
- >85% β-blockers
- >90% ACEI/ARB
- 10% device therapy
- Exclusion: GFR <30, K > 5.0
- Eplerenone 50mg od (40mg)
- Labs q 4 months
- All cause mortality reduced
- More hyperkalemia
- Less hypokalemia

Zannad, F, et al. NEJM 2011; 364:11-21

**Aldosterone Receptor Blocker: Guideline- Based Recommendation**

**Chronic Heart Failure (pHFA)**

- **2012 update**
- Recommended for pts with: Class III/IV HF with reduced LVEF ≤ 35% while receiving standard therapy with ACEi and BB to reduce M&M
- Prior HF hospitalization or elevated BNP

**Post MI HF (HFSA)**

- Recommended for pts post MI, and LVEF ≤ 40%, with either clinical HF or DMI for reducing M&M

**Contraindications**
- Not recommended:
  - Creatinine >2.5 (men) or >2.0 (women) mg/dl or GFR < 30 ml/min/1.73 m2
  - K ≥ 5.5 mmol/L
  - In conjunction with other potassium-sparing diuretics
  - Avoid NSAIDs

**Monitoring**
- Careful monitoring of K, renal function and diuretic dose
- Measure K: 3 days, 1 wk, at least monthly for the first 3 mos
- Discontinue or reduce supplemental K (eg. Unless K persistently < 4.0 mEq/L)
Hydralazine- Isosorbide Dinitrate combo: The A-HeFT Trial

- 1050 NYHA III/IV AA pts
- Reduced LVEF or dilated LV
- Composite endpt: death, HF hosp, QOL (all of the components improved)
- Terminated early
- Bid (Hydralazine 37.5mg+ Isordil 20mg) 2 tablets tid
- Contemporary Background to
- Adverse events: common - HA 44%, dizziness 29%

63% reduction to RR in mortality

Hydralazine-Isordil combination: Guideline-Based Recommendations

The combination of hydralazine and isosorbide dinitrate is recommended for AA with NYHA class III–IV HF/EF on GDMT (I, A)

A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF/EF who cannot be given ACE inhibitors or ARBs (IIa, B)

Digoxin

Digoxin can be beneficial in patients with HF/EF (IIa, B)

Effects of Digoxin and Serum Drug Level


Adams, et al. JACC 2002;39:946
Mechanism of action

- Primary mechanism of action involves inhibition of the Na+/K+ ATPase, mainly in the myocardium.
- The inhibition of the sodium pump may also improve baroreceptor sensitivity in HF and may explain some of the neurohormonal effects of digoxin.
- Digoxin has important parasympathetic effects, particularly on the atrioventricular node.

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Digoxin:
Guideline-Based Recommendations

<table>
<thead>
<tr>
<th>Chronic Heart Failure</th>
<th>Considered for patients with LVEF ≤ 40% and current or prior HF signs/symptoms, to decrease HF hospitalizations (Class IIa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>Dose based on lean body mass, renal function, age, and concomitant meds: 0.125 to 0.25mg daily (0.125mg daily in the vast majority of pts)</td>
</tr>
<tr>
<td></td>
<td>• No loading dose is required</td>
</tr>
<tr>
<td></td>
<td>• Adverse event rates increased in hypokalemia, hypomagnesemia or hypothyroidism</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>Reasonable – If BB alone is not effective (digoxin less effective during exercise)</td>
</tr>
<tr>
<td></td>
<td>• High doses (maintenance dose &gt; 0.25mg daily) for the purpose of rate control in AF are not recommended (HFSA)</td>
</tr>
</tbody>
</table>

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Pharmacokinetics of Diuretic Drugs

[Diagram of Pharmacokinetics of Diuretic Drugs]
Diuretics:
Guideline-Based Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diuretics: indications for fluid overload, unless contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater diuresis</td>
<td>Diuretics: indications for fluid overload, unless contraindicated</td>
</tr>
<tr>
<td></td>
<td>Diuretic refractoriness: cardio-renal effects, progressive cardiac dysfunction, non-compliance, (IV)DSS</td>
</tr>
<tr>
<td></td>
<td>Increase dose to 2 or 3 times daily dosing: provides more diuresis with less physiologic perturbation than larger single dose</td>
</tr>
<tr>
<td></td>
<td>Consider switching to oral torsemide</td>
</tr>
<tr>
<td></td>
<td>Consider adding chlorothiazides or metolazone</td>
</tr>
<tr>
<td></td>
<td>IV administration</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitor for electrolyte abnormalities, symptomatic hypotension, renal dysfunction (esp high dose, combo dosing)</td>
</tr>
<tr>
<td>Treatment goal</td>
<td>Chronic treatment usually required, often at lower dose</td>
</tr>
<tr>
<td></td>
<td>Consider dose reduction or even discontinuation in pts with improved clinical status and cardiac function</td>
</tr>
<tr>
<td></td>
<td>Monitor carefully for recurrent fluid retention</td>
</tr>
<tr>
<td>Pt Education</td>
<td>Weight and fluid monitoring</td>
</tr>
<tr>
<td></td>
<td>Selected pts may adjust dose to weight/clinical change</td>
</tr>
</tbody>
</table>

Ivabradine

- U.S. Food and Drug Administration approved Ivabradine in April 2015
- To reduce hospitalization from worsening heart failure.
- Use in HF patients: stable, symptomatic chronic heart failure LVEF ≤ 35%, in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
- Contraindications: Acute decompensated heart failure, Blood pressure < 90/50 mmHg, Sick sinus syndrome, sinoatrial block or 3 rd degree AV block [unless a functioning demand pacemaker is present], Resting heart rate < 60 bpm prior to treatment, Severe hepatic impairment, Pacemaker dependence (heart rate maintained exclusively by the pacemaker)

Ivabradine

- Warnings & Precautions: Fetal toxicity, monitor patients for atrial fibrillation, monitor for decrease in heart rate and bradycardia symptoms during treatment. Not recommended in patients with 2 nd degree AV block
- Drug Facts/ Pharmacology: First-in-class to selectively and specifically inhibit hyperpolarization-activated cyclic nucleotide (HCN) gated (If current) channel within the SA node that lowers heart rate. It causes a dose-dependent reduction in heart rate. Size of the effect is dependent on the baseline heart rate.
Ivabradine

- Drug Interactions: Any CYP3A4 inhibitors or inducers.
- Moderate risk QTc-prolonging agents, may enhance the QTc prolonging effect
- Any agents that enhance the bradycardic effects
- Common Adverse Effects: Bradydcardia, Atrial Fibrillation, visual brightness, hypertension
- Recommended starting dose: 5mg tablet by mouth twice daily with meals or 2.5mg tablet by mouth twice daily for patients in whom bradycardia could lead to hemodynamic compromise or with a history of conduction defects. After 2 weeks, check

Inotropic support
Milrinone

- Phosphodiesterase type 3 inhibitor
- Increase contractility (improves cardiac output) and decrease pulmonary vascular resistance
- Vasodilator; which helps alleviate increased pressures (afterload reduction) on the heart, thus improving cardiac output

Milrinone

- Cyclic adenosine monophosphate (cAMP) causes increased activation of protein kinase A (PKA). PKA is an enzyme that phosphorylates many elements of the contractile machinery within the myocyte
- This leads to an increased force of contraction. Phosphodiesterase are enzymes responsible for the breakdown of cAMP. Therefore when phosphodiesterases lower the level of cAMP in the cell they also lower the active fraction of PKA within the cell and reduce the force of contraction.

Dobutamine

- Direct-acting inotropic agent
- Primary activity results from stimulation of the β receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects.
- It does not cause the release of endogenous norepinephrine, as does dopamine.
Dopamine

- An endogenous central neurotransmitter, immediate precursor to norepinephrine in the catecholamine synthetic pathway.
- When administered therapeutically, it acts on dopaminergic and adrenergic receptors to elicit a multitude of clinical effects.
- At low doses (0.5 to 3 mcg/kg/min), stimulation of dopaminergic D₁ postsynaptic receptors concentrated in the coronary, renal, mesenteric, and cerebral beds and D₂ presynaptic receptors present in the vasculature and renal tissues promotes vasodilation and increased blood flow to these tissues.
- Dopamine also has direct natriuretic effects through its action on renal tubules. The clinical significance of “renal-dose” dopamine is somewhat controversial, however, because it does not increase glomerular filtration rate and a renal protective effect has not been demonstrated.
- At intermediate doses (3 to 10 mcg/kg/min), dopamine weakly binds to β₁-adrenergic receptors, promoting norepinephrine release and inhibiting reuptake in presynaptic sympathetic nerve terminals, which results in increased cardiac contractility and chronotropy, with a mild increase in SVR.
- At higher infusion rates (10 to 20 mcg/kg/min), α₁-adrenergic receptor-mediated vasoconstriction dominates.

Management of Heart Failure

Summary

- ACE inhibitors remain the cornerstone of therapy.
- However, recent PARADIGM-HF study indicates improved outcome with sacubutril/valsartan combo.
- Beta blockers: carefully titrate to goal doses in stable pts.
- Aldosterone antagonists: indicated in symptomatic systolic heart failure.
- Digoxin is a useful adjunct to improve symptoms (does not improve mortality).
- ARBs are useful in ACEI/sacubutril/valsartan intolerant patients.
- Inotropic and vasopressor support when needed.
- HF hospitalizations are ominous and may be best prevented by a disease management multidisciplinary team.

QUESTIONS ???

Thank you