Contemporary Management of Heart Failure

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Comprehensive Heart Failure Management Program
BHHI Primary Care Symposium
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DISCLOSURES

• I have no disclosures
OUTLINE

• DEFINITION OF HEART FAILURE

• SIGNS and SYMPTOMS

• CLASSIFICATION OF HEART FAILURE

• NON-PHARMACOLOGICAL THERAPY

• PHARMACOLOGICAL THERAPY
Defining Heart Failure

• “Congestive” heart failure has been replaced with simply - Heart Failure
  • recognition that many patients are not “congested”

• Complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood

• Heart Failure with Reduced Ejection Fraction (HFrEF)
  • LVEF ≤ 40%

• Heart Failure with Preserved Ejection Fraction (HFpEF)
  • LVEF ≥ 50%
Cardinal Signs and Symptoms

- Dyspnea
- Fatigue
- Orthopnea
- Peripheral edema
- Paroxysmal Nocturnal Dyspnea (PND)
- Exercise Intolerance
- Anorexia / Early Satiety
- Cold Extremities

- Pitting edema
- Elevated Jugular Venous Pressure
- Cardiomegaly
- Third Heart Sound / S3 Gallop
- Rales / crackles
- Hepatomegaly
- Ascites
# Classification of Heart Failure

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> At high risk for HF but without structural heart disease or symptoms of HF.</td>
<td>None</td>
</tr>
<tr>
<td><strong>B</strong> Structural heart disease but without signs or symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td><strong>C</strong> Structural heart disease with prior or current symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td><strong>D</strong> Refractory HF requiring specialized interventions.</td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>
Stages, Phenotypes and Treatment of HF

**At Risk for Heart Failure**

- **STAGE A**
  - At high risk for HF but without structural heart disease or symptoms of HF
  - e.g., Patients with:
    - HTN
    - Atherosclerotic disease
    - DM
    - Obesity
    - Metabolic syndrome or
      - Patients
        - Using cardiotonics
        - With family history of cardiomyopathy
  - THERAPY
    - Goals
      - Heart healthy lifestyle
      - Prevent vascular, coronary disease
      - Prevent LV structural abnormalities
    - Drugs
      - ACEI or ARB in appropriate patients for vascular disease or DM
      - Statins as appropriate

- **STAGE B**
  - Structural heart disease but without signs or symptoms of HF
  - e.g., Patients with:
    - Previous MI
    - LV remodeling including LVH and low EF
    - Asymptomatic valvular disease
  - Development of symptoms of HF
  - THERAPY
    - Goals
      - Prevent HF symptoms
      - Prevent further cardiac remodeling
    - Drugs
      - ACEI or ARB as appropriate
      - Beta blockers as appropriate
    - In selected patients
      - ICD
      - Revascularization or valvular surgery as appropriate

**Heart Failure**

- **STAGE C**
  - Structural heart disease with prior or current symptoms of HF
  - e.g., Patients with:
    - Known structural heart disease and HF signs and symptoms
  - THERAPY
    - Goals
      - Control symptoms
      - Patient education
      - Prevent hospitalization
      - Prevent mortality
    - Drugs for routine use
      - Diuretics for fluid retention
      - ACEI or ARB
      - Beta blockers
      - Aldosterone antagonists
    - Drugs for use in selected patients
      - Hydralazine/isosorbide dinitrate
      - ACEI and ARB
      - Digoxin
    - In selected patients
      - CRT
      - ICD
      - Revascularization or valvular surgery as appropriate

- **STAGE D**
  - Refractory HF
  - e.g., Patients with:
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT
  - THERAPY
    - Goals
      - Control symptoms
      - Patient education
      - Prevent hospitalization
      - Prevent mortality
    - Drugs for routine use
      - Diuretics for fluid retention
      - ACEI or ARB
      - Beta blockers
      - Aldosterone antagonists
    - Drugs for use in selected patients
      - Hydralazine/isosorbide dinitrate
      - ACEI and ARB
      - Digoxin
    - In selected patients
      - CRT
      - ICD
      - Revascularization or valvular surgery as appropriate

ACC / AHA Guidelines 2013
A Brief Word About Heart Failure with Preserved Ejection Fraction

• No specific therapies have demonstrated significant benefit

• **Primary Importance** – control of both Systolic and Diastolic BP
  - BP control → reduced hospitalization for HF, reduced CV events and HF mortality in all populations

• Management of other contributory risk factors and co-morbidities including:
  - Diabetes Mellitus
  - Coronary Artery disease / ischemia
  - Dyslipidemia
  - Atrial Fibrillation

• Identical Dietary and Life-Style modifications to Heart Failure with Reduced EF (HFrEF)

• Use of Guideline Directed Medical Therapies (GDMT) – beta-blockers, ACE inhibitors and Angiotensin receptor blockers for the treatment of hypertension

• Diuretics for congestion
Management of Stage C Heart Failure

• Non-pharmacologic therapies
• Pharmacologic Therapies
  • Beta-blockers
  • Ivabradine (Corlanor®)
  • ACEI / ARB
  • Valsartan – Sacubitril (Entresto®)
• Mineralocorticoid Receptor Antagonists
• Hydralazine / Isosorbide Dintrate
• Digoxin
• Diuretics
• Device Therapies
Non-Pharmacologic Therapies

• Sodium Restriction < 2500 mg / day
• Fluid Restriction < 1.5 L to 2 L
• Healthy Life-style Modifications
• Weight Loss
• Patient Education

Cardiac Rehabilitation / Graded Exercise Program

• Improves functional status
• Improves quality of life
• Reduces Hospitalizations
  • Reduces Mortality
Pharmacologic Therapies
Guideline Directed Medical Therapies (GDMT)

General Order of Initiation and Titration:

1. ACEI / ARB*
2. Beta-blockers*
3. Mineralocorticoid Receptor Blockers
4. Hydralazine – Isosorbide Dinitrate
5. Digoxin
6. Diuretics – for treatment of congestion and symptoms

* Typically start and titrate BB and ACEI / ARB concomitantly
Angiotensin Converting Enzymes Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)

- Recommended in ALL patients with Stage C HF

<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>50mg TID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>40mg QD (20mg BID)</td>
</tr>
<tr>
<td>Quinapril</td>
<td>20mg BID</td>
</tr>
<tr>
<td>Ramipril</td>
<td>10mg QD</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4mg QD</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>40mg QD</td>
</tr>
<tr>
<td>Peridopril</td>
<td>8mg QD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARB</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>32mg QD</td>
</tr>
<tr>
<td>Losartan</td>
<td>150mg QD</td>
</tr>
<tr>
<td>Valsartan</td>
<td>160mg BID</td>
</tr>
</tbody>
</table>

- Alternative for patients intolerant to ACEI
- Caution in patients with ACEI induced Angioedema

- Considered class effect
- Titration concomitantly with BB
Considerations for ACEI / ARB Therapy

- Titrate every 2 weeks to achieve maximum tolerated doses
- Caution in:
  - Hypotension, SBP < 85 mmHg
  - Elevated Serum Creatinine > 3 mg/dL
  - Bilateral renal artery stenosis
  - Hyperkalemia K+ > 5
  - Hyponatremia – can exacerbate hypotension
- Monitor renal function and potassium at baseline and every 1-2 weeks during titration
- Combination of ACEI + ARB is NOT recommended
- Triple therapy with ACEI + ARB + Aldosterone blockade is not recommended d/t risk of Hyperkalemia
Valsartan – Sacubitril (Entresto ®)

- Neprilysin is an endopeptidase that degrades vasoactive peptides: natriuretic peptides, bradykinin and adrenomedullin
- **Sacubitril** – inhibits Neprilysin → increasing activity of vasoactive peptide
  - Vasodilation
  - Sodium excretion
  - Counteract the upregulated RAAS
  - Reduce sympathetic activity
  - Reduces fibrosis and maladaptive cardiac remodeling
  - Anti-proliferative and anti-hypertrophic effects
PARADIGM-HF Trial

- Compared valsartan-sacubitril to enalapril in patients with HFrEF and NYHA Class II-IV

**Table 2. Primary and Secondary Outcomes.***

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function§</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Entresto ® demonstrated:**

- 20% reduction in composite of CV death or HF hospitalization
- 20% reduction in CV death
- 21% reduction in Heart Failure hospitalization

McMurray JJV et al. NEJM 2014.
Considerations for Entresto ® Therapy

- If on ACEI – discontinue for 36 hrs prior to starting Entresto
- Starting dose: 24/26 mg BID
  - Prescribing insert suggests starting 49/51mg BID if already on ACEI / ARB
  - However I recommend always starting with 24/26mg BID
- Titrate every 2 weeks
  - Monitor BP, renal function and potassium weekly during titration
  - I recommend clinic visits every 2 weeks prior to increased titration
- Subsequent doses: 49/51mg BID and 97/103mg BID

Cautions / Contraindications:

- GFR < 30 mL/min/m2
- Moderate hepatic impairment
- Fetal toxicity
- Angioedema

Monitor for:
- Hypotension
- Hyperkalemia
- Cough (increased bradykinin)
## Beta-antagonists

<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Starting Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol (Zebeta®)</td>
<td>2.5 – 5mg Daily</td>
<td>10mg daily</td>
</tr>
<tr>
<td>Carvedilol (Coreg®)</td>
<td>3.125mg – 6.25mg BID</td>
<td>25mg BID (&lt;85kg)</td>
</tr>
<tr>
<td>Carvedilol CR (Coreg CR®)</td>
<td>10mg Daily</td>
<td>80mg Daily</td>
</tr>
<tr>
<td>Metoprolol succinate (Toprol XL®)</td>
<td>25mg – 50mg Daily</td>
<td>200mg Daily</td>
</tr>
</tbody>
</table>
Considerations for Beta-blocker Therapy

- Start in all *Compensated* Heart Failure Stage B-D
- Start LOW and Go SLOW – titrate at 2 week intervals
- Achieve goal doses used in Randomized Controlled Trials
  - Goal HR: 60-70
- Do NOT discontinue during acute decompensation unless severe hypotension
- Guidelines do not recommend one BB over another
  - Consider Carvedilol for:
    - EF < 25%
    - Persistent Hypertension
  - Consider Metoprolol Succinate
    - Unable to achieve target HR due to hypotension
    - Unable to achieve target dose due to hypotension
IVABRADINE (Corlanor ®)

- If Channel inhibitor → reduces sinoatrial (SA) firing → reduces HR without other CV effects
- Indications:
  - NYHA Class II-IV
  - Symptomatic
  - Sinus Rhythm
  - Heart Rate > 70 bpm
  - On maximum tolerated doses of BB or contraindication to BB

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 bpm</td>
<td>2.5 mg BID</td>
<td>Increase every 2 weeks by 2.5mg Max dose: 7.5mg</td>
</tr>
<tr>
<td>50 – 60 bpm (Target Heart Rate)</td>
<td>5mg BID</td>
<td>No change, monitor resting heart rate</td>
</tr>
<tr>
<td>&lt; 50 bpm</td>
<td>Do not start</td>
<td>Decrease does by 2.5mg BID or discontinue</td>
</tr>
</tbody>
</table>
SHIFT Trial

- Mean HR 65 bpm in Ivabradine group compared to 75 bpm in control group
- Ivabradine Therapy resulted in:
  - 26% reduction in hospitalization due to Heart Failure
  - 26% reduction in Heart Failure deaths
  - 18% reduction in composite of hospitalization or CV death

(Swedberg K et al. Lancet 2010)
Considerations for Ivabradine Therapy

- Adverse Events: bradycardia, hypertension, new onset atrial fibrillation, visual brightness
- Contraindications:
  - Acute decompensated heart failure
  - Hypotension: BP < 90 / 50 mmHg
  - Conduction disturbances:
    - Sick sinus syndrome
    - SA node dysfunction
    - 3rd degree AV block
    - HR < 60 bpm
- Increased incidence of New Onset Atrial fibrillation
  - 8.3% vs. 6.6%
- Concurrent use with diltiazem or verapamil increases risk of symptomatic bradycardia
Mineralocorticoid Receptor Antagonists (MRA)

- Recommended in:
  - NYHA Class II – IV with EF ≤ 35%
  - After Acute MI with EF ≤ 40% or DM

<table>
<thead>
<tr>
<th>Pharmacodynamics</th>
<th>Eplerenone (Inspra®)</th>
<th>Spironolactone (Aldactone®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Dose</td>
<td>50mg daily</td>
<td>25mg daily</td>
</tr>
<tr>
<td>Gyencostasia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Indication</td>
<td>NYHA Class II- IV, HF post-MI, HTN</td>
<td>NYHA Class II-IV, HTN</td>
</tr>
</tbody>
</table>
Considerations for MRA Therapy

- Reduced dosing when initiating in patients with renal insufficiency
  - CrCl 30-49 → every other day dosing
  - CrCl < 30 → not recommended
- Discontinue Potassium supplements
- Educate patients to hold if episode of diarrhea
- Monitor renal function and potassium:
  - Baseline, 1 week, monthly x3, every 3 months
- Discontinue if Serum Cr ≥ 5.5

- Contraindicated / Not Recommended:
  - SCr > 2 females / SCr > 2.5 males
  - CrCl < 30
  - Serum K+ > 5
Hydralazine-Isosorbide Dinitrate

- Class I for African Americans with NYHA Class III – IV HF
  - After on maximum doses of GDMT including: BB, ACEI / ARB and MRA
- No clear benefit in non-African Americans
- Can use for patients intolerant to ACEI /ARB due to hypotension, allergy or renal failure
- Consider in patients who remain symptomatic on maximum GDMT

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine and Isosorbide dinitrate (generic individual drugs)</td>
<td>75mg QID + 40mg QID</td>
</tr>
<tr>
<td>BiDIL ® [37.5 mg / 40mg]</td>
<td>2 tablets TID</td>
</tr>
</tbody>
</table>

- May see benefit in patients that require greater afterload reduction
Digoxin

- Adjunct therapy
- Improved symptoms
- Decreased hospitalizations
- No mortality or morbidity benefit
- Dose: 0.125 mg – 0.25 mg QD
  - Target Level < 1ng/mL
- Increased Risk of Toxicity:
  - Hypokalemia
  - Hypomagnesemia
  - Hypothyroidism
- Caution in Elderly (typically don’t use > 65 yrs of age)
- Watch for Drug-drug interaction
Diuretic Therapy

- Symptomatic treatment → GOAL is to eliminate excess fluid
- No demonstrable mortality benefit
- Used in all patients with congestion / volume overload
- Loop diuretics are the MAINSTAY of diuretic therapy

<table>
<thead>
<tr>
<th>Loop Diuretic</th>
<th>Initial Daily Dose(s)</th>
<th>Max Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5 – 1.0 mg qd/bid</td>
<td>10 mg</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 – 40 mg qd/bid</td>
<td>600 mg</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 – 20 mg qd</td>
<td>200 mg</td>
<td>12-16 hours</td>
</tr>
</tbody>
</table>

Equivalent dosing: Furosemide 40mg = Bumetanide 1mg = Torsemide 20mg
Diuretic Resistance

- The failure to decrease the extracellular fluid volume despite liberal use of diuretics
- Multiple possible physiological reasons: worsening heart failure, neurohormonal upregulation, dietary indiscretion, renal insufficiency, decreased absorption etc....

Strategies to overcome Diuretic Resistance

- Increase oral dose – double each dose (40mg BID → 80mg BID)
- Change loop diuretic – furosemide → bumetanide
- Addition of Thiazide-type diuretic (synergistic effect)
  - Metolazone 2.5 – 10mg PRN or 2-3 days weekly
  - Chlorothiazide 250 – 500mg PRN
- Strict Sodium restriction
- Avoid NSAID use
- IV administration – often 1-2 doses can decongest the gut and improve absorption
  - Can consider Diuretic Infusion suite for refractory cases
SUMMARY for STAGE C HF

• Initiation and titration to maximum tolerated doses of GDMT
  • Start and titrate BB and ACEI simultaneously
  • Then add MRA, Hydral-Isoordil, digoxin in stepwise fashion
  • Consider Valsartan-Sacubitril and Ivabradine in appropriate patients

• Titrate GDMT every 2 weeks

• Frequent contact with providers and staff – I see pts every 2 weeks when aggressively titrating GDMT

• Goal is to achieve NYHA Class I Functional Class

Target BP – lowest tolerated by patient (90/60 – gen. rule)
Target HR – 50-60 bpm
SUMMARY for STAGE C HF

• Cardiac Rehabilitation and / or Graded Exercise Program
  ➢ Improves functional status, reduces HF hospitalizations, improves quality of life and reduces CV mortality

• Diuretic Resistance
  • Increase oral dose
  • Alternative Loop Diuretic
  • Add Thiazide
  • Intermittent IV dosing

Most Importantly ➔ Life-Style Modifications
  • Daily weights
  • Daily home Blood Pressure
  • Sodium restriction
  • Weight loss
  • Healthy diet
One of the Most Important Devices for Monitoring Heart Failure
Thank you!

QUESTIONS?
References

1. Yancy et al. 2013 ACCF / AHA Heart Failure Guidelines. JACC 2013; (62) e147-e239