Contemporary Management of Heart Failure

Keerthy K Narisetty, MD
Comprehensive Heart Failure Management Program
BHBI Primary Care Symposium

Disclosures

I have no relevant relationships with commercial interests to disclose.
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>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>D 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>
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</tbody>
</table>

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

Piepoli MF et al. / Pina IL et al. / Austin J et al.
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>
<th>ARB</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>50mg TID</td>
<td>Candesartan</td>
<td>32mg QD</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10mg BID</td>
<td>Losartan</td>
<td>150mg QD</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>40mg QD (20mg BID)</td>
<td>Valsartan</td>
<td>160mg BID</td>
</tr>
<tr>
<td>Quinapril</td>
<td>20mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>10mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>40mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peridopril</td>
<td>8mg QD</td>
<td></td>
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</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

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) – 50mg BID (&gt;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>
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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 ®)

- I$_c$ 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</td>
</tr>
<tr>
<td></td>
<td>Max dose: 7.5mg</td>
<td></td>
</tr>
<tr>
<td>50 – 60 bpm</td>
<td>5mg BID</td>
<td>No change, monitor resting heart rate</td>
</tr>
<tr>
<td>(Target Heart Rate)</td>
<td></td>
<td></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>Gyencomastia</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</td>
<td>75mg QID + 40mg QID</td>
</tr>
<tr>
<td>(generic individual drugs)</td>
<td></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-Isordil, 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

Monitoring Devices- CARDIOMEMS
Thank You

References

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