



## Contemporary Management of Heart Failure

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## 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  $\leq$  40%
- Heart Failure with Preserved Ejection Fraction (HFpEF)
  - LVEF  $\geq$  50%

## Cardinal Signs and Symptoms

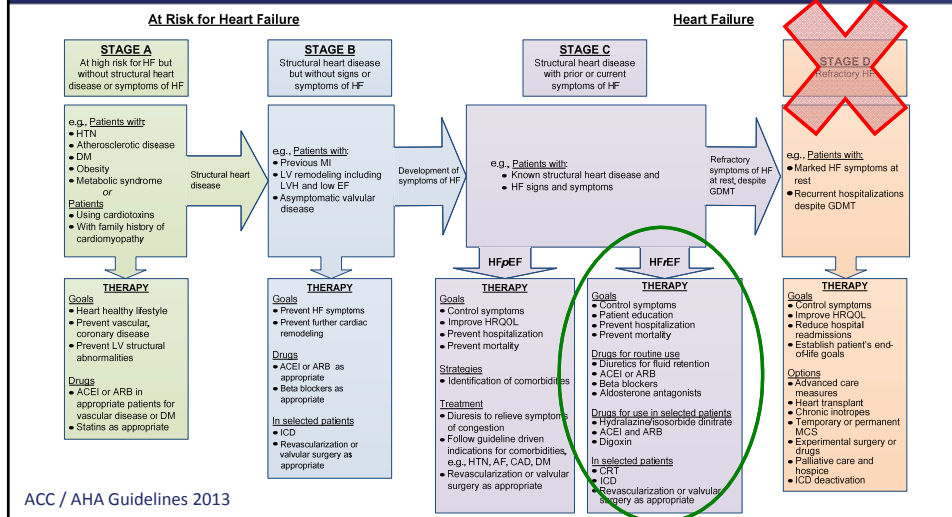
- Dyspnea
- Fatigue
- Orthopnea
- Peripheral edema
- Paroxysmal Nocturnal Dyspnea (PND)
- Exercise Intolerance
- Anorexia / Early Satiety
- Cold Extremities
- Pitting edema
- Elevated Jugular Venous Pressure
- Cardiomegaly
- Third Heart Sound / S3 Gallop
- Rales / crackles
- Hepatomegaly
- Ascites

## Classification of Heart Failure

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	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.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.		

ACC / AHA Guidelines 2013

# Stages, Phenotypes and Treatment of HF



## 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 Dinitrate
  - 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

ACE Inhibitor	Target Dose
Captopril	50mg TID
Enalapril	10mg BID
Lisinopril	40mg QD (20mg BID)
Quinapril	20mg BID
Ramipril	10mg QD
Trandolapril	4mg QD
Fosinopril	40mg QD
Perindopril	8mg QD

ARB	Target Dose
Candesartan	32mg QD
Losartan	150mg QD
Valsartan	160mg BID

- Considered class effect
- Titration concomitantly with BB

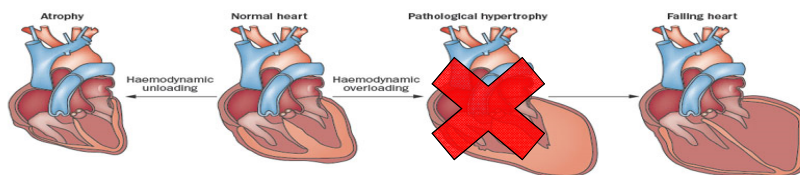
- Alternative for patients intolerant to ACEI
- Caution in patients with ACEI induced Angioedema

## 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

McMurray JJV et al. NEJM 2014.

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

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

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	-2.99±0.36	-4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

### Entresto® demonstrated:

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

## 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:

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• GFR &lt; 30 mL/min/m<sup>2</sup></li> <li>• Moderate hepatic impairment</li> <li>• Fetal toxicity</li> <li>• Angioedema</li> </ul> | <p>Monitor for:</p> <ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Hyperkalemia</li> <li>• Cough (increased bradykinin)</li> </ul> |
|---|---|



## Beta-antagonists

Beta-Blocker	Starting Dose	Target Dose
Bisoprolol (Zebeta®)	2.5 – 5mg Daily	10mg daily
Carvedilol (Coreg®)	3.125mg – 6.25mg BID	25mg BID (<85kg) 50mg BID (>85kg)
Carvedilol CR (Coreg CR®)	10mg Daily	80mg Daily
Metoprolol succinate (Toprol XL®)	25mg – 50mg Daily	200mg Daily

## 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<sub>f</sub> 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

Heart Rate	Dose	Titration
> 60 bpm	2.5 mg BID	Increase every 2 weeks by 2.5mg Max dose: 7.5mg
50 – 60 bpm (Target Heart Rate)	5mg BID	No change, monitor resting heart rate
< 50 bpm	Do not start	Decrease does by 2.5mg BID or discontinue

## SHIFT Trial

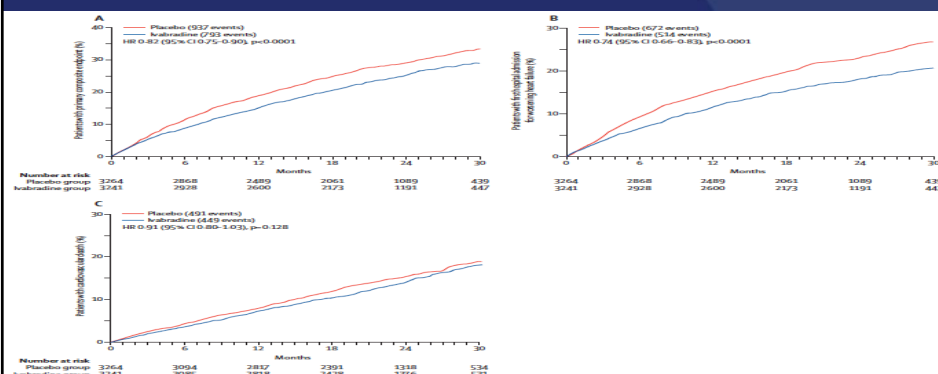


Figure 3: Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death

- 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

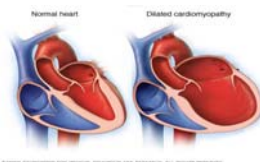
- Adverse Events: bradycardia, hypertension, new onset atrial fibrillation, visual brightness
- Contraindications:
  - Acute decompensated heart failure
  - Hypotension: BP < 90 / 50 mmHg
  - Conduction disturbances:
    - Sick sinus syndrome
    - SA node dysfunction
    - 3<sup>rd</sup> degree AV block
    - 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  $\leq$  35%
  - After Acute MI with EF  $\leq$  40% or DM

	Eplerenone (Inspra®)	Spironolactone (Aldactone®)
Pharmacodynamics	Selective MRA	Non-Selective MRA
Target Dose	50mg daily	25mg daily
Gynecomastia	No	Yes
Indication	NYHA Class II- IV, HF post-MI, HTN	NYHA Class II-IV, HTN



## 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  $\geq$  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

Therapy	Target Dose
Hydralazine and Isosorbide dinitrate (generic individual drugs)	75mg QID + 40mg QID
BiDIL ® [37.5 mg / 40mg]	2 tablets TID

- 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

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

**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

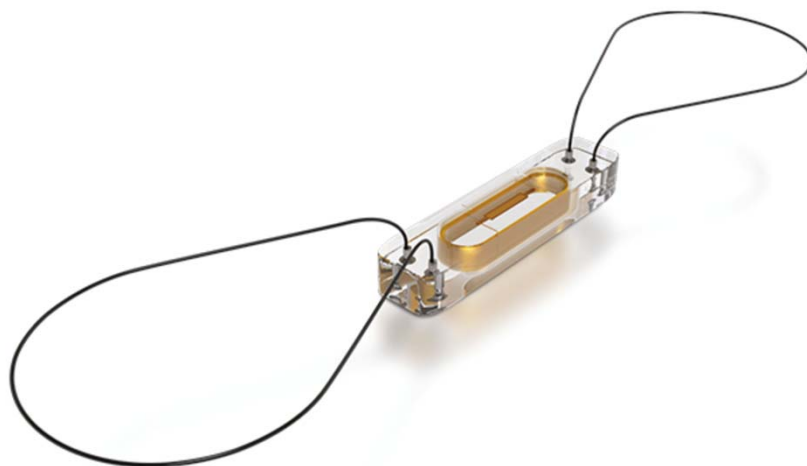
Most Importantly → Life-Style Modifications

- 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





# HEART MATE 3



# Thank You

## References

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