

Heart Failure: Refreshers & Updates

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Disclosure Statement

- I have no relevant financial relationships or commercial interests to disclose in conjunction with this presentation.

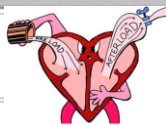
Objectives

- Explain the complexity of the pathophysiology of CHF including compensatory mechanisms.
- Recognize the drugs used and describe their appropriate role in treatment of heart failure with reduced ejection fraction (HFrEF).
- Review new drug options available to treat HFrEF.

Chronic Heart Failure (CHF)

- A clinical syndrome resulting from any disorder that
 - Impairs the ability of the ventricle to fill with (diastole) or eject blood (systole)
 - Heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body
- Previously defined as Congestive Heart Failure
- **Cardiac Output = Heart rate x Stroke Volume**
 - $CO = HR \times SV$

Definitions



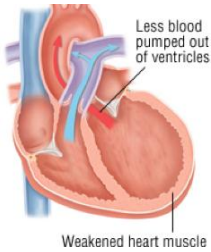
- **Afterload**
 - Tension developed in the left ventricular wall as systole occurs
 - Regulated by systemic vascular resistance or the impedance which the left ventricle must pump against
 - Mainly determined by arterial blood pressure
- **Preload**
 - Volume in the left ventricle at the end of diastole (relaxation)

Terms

- **Frank-Starling Mechanism**
 - Describes the ability of the heart to alter the force of contraction depending on preload
 - In a dysfunctional ventricle, sarcomeres are stretched too far limiting the ability to contract
- **Ejection Fraction (EF)**
 - The percentage of left ventricular blood volume "ejected" during systole (contraction)
 - Normal EF is 60% to 70%
- **Right-sided & left-sided HF**
 - Anatomical

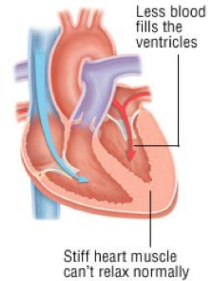
HFrEF (Systolic Dysfunction)

- Low EF <40%
- Unable to eject enough blood to keep up with the metabolic demands of the body
- Ventricle has difficulty contracting → ventricles become dilated → congeste with retained blood
- Most common cause of systolic heart failure
 - MI (CAD)



HFpEF (Diastolic Dysfunction)

- Associated with an EF >40%
- Ventricle has diastolic stiffness
 - Reduced compliance
 - Unable to fill adequately
- Most common cause of diastolic heart failure is hypertension
 - Therapy aimed at heart rate & blood pressure control



HFrEF

Heart Failure with Reduced Ejection Fraction

Pathophysiology

- Compensatory Mechanisms
 - Intended to be short term responses
 - Maintain circulatory homeostasis after acute reductions in blood pressure or renal perfusion
 - Detrimental long term
 - May occur after an acute or chronic event
- Neurohormonal Model
 - Sympathetic nervous system (SNS)
 - Renin-Angiotensin-Aldosterone System (RAAS)

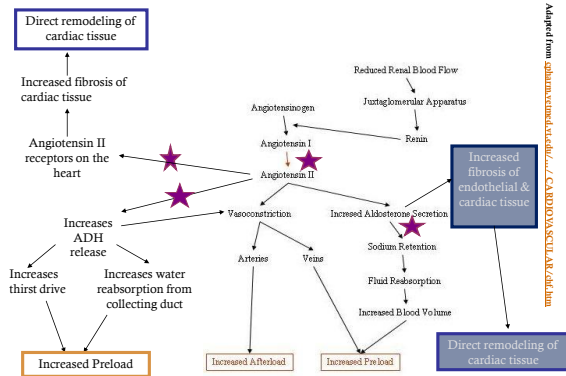
SNS

- Causes tachycardia
 - Tries to increase CO by increasing HR
 - Causes increase in oxygen demand
 - Eventually decreases filling time actually decreases SV
- Increases contractility
 - Tries to increase CO by increasing SV
 - Causes increase in oxygen demand

Beta Receptors

- Overstimulation of β receptors
 - Causes a down regulation and \downarrow synthesis of
 - Initiates "uncoupling" of receptors
- Blunting of the sympathetic response in a failing heart
 - Unable to respond to environmental stressors
 - These changes in receptor dynamics are important when initiating beta blockers and especially in a decompensated state

Renin Angiotensin Aldosterone System



Treatments

- Treatment of HFrEF focuses on
 - Manipulation of SNS & RAAS
 - Management of concomitant disease states
 - Lifestyle changes / management
- HF guidelines (2013)
 - <http://circ.ahajournals.org/content/128/16/e240>
- Update (2016)
 - <http://circ.ahajournals.org/content/circulationaha/early/2016/05/18/CIR.000000000000435.full.pdf>

Presentation

Signs	Symptoms
<ul style="list-style-type: none"> ▪ Pulmonary rales ▪ Lower leg edema ▪ Jugular venous distention ▪ Increase BNP 	<ul style="list-style-type: none"> ▪ Dyspnea (on exertion) ▪ Orthopnea ▪ Paroxysmal nocturnal dyspnea ▪ Edema ▪ Fatigue ▪ Exercise intolerance

Current Treatments

“Live Longer” Medications	“Feel Better” Medications
<ul style="list-style-type: none"> ▪ Shown to improve mortality ▪ Beta-Blockers ▪ ACE-I ▪ ARB ▪ Aldosterone Antagonists ▪ Hydralazine & isosorbide dinitrate ▪ *Sacubitril / valsartan 	<ul style="list-style-type: none"> ▪ No benefit on mortality ▪ Can help with hospitalizations ▪ Diuretics <ul style="list-style-type: none"> • Loop • Thiazide (Metolazone) ▪ Digoxin ▪ *Ivabradine

“Live Longer” Medications

β Blockers

- Cornerstone for patients with HFrEF
 - Start as soon as diagnosed (studied NYHA II-IV)
- Will increase ejection fraction
 - Especially if due to ischemic causes
- MOA
 - Decreases contractility (acutely)
 - “Resets” β receptors
 - Decreases cardiac remodeling; allowing the heart to return to normal or near normal functioning
- **NDP CCB are NOT an alternative

Drugs & Dosing

<i>Drug Name</i>	<i>Initial Dose</i>	<i>Target Dose</i>
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily (50 mg twice daily if >85 kg)
Metoprolol succinate	12.5 – 25 mg daily	200 mg daily

- β blockers should NOT be started too quickly
 - Start only in stable, euvolemic patients
- Start low and go slow
- Titrate every 2-4 weeks if stable
 - Dose usually doubled
 - Stop at max dose

ADR: Educate!

- May worsen symptoms at first
- Four main ADR that require attention
 - Fluid retention & worsening HF
 - Fatigue
 - Bradycardia
 - Hypotension
- \downarrow Quality of Life
 - \uparrow fatigue
 - Exacerbate depression
 - Decrease libido/ED
- Constant monitoring
 - Symptoms
 - BP, HR

ACE-Inhibitors

- Recommended for all pts with HFrEF
- Improve symptoms and exercise tolerance
- MOA in HF
 - Decrease preload
 - \downarrow Na & H₂O retention \rightarrow \downarrow blood volume
 - Decrease afterload (\downarrow arteriole pressure)
 - Postulated vasodilation benefits of bradykinin & PG
 - Cardiac remodeling
 - \downarrow hypertrophy, fibrinogen, & collagen in cardiac myocyte

Drugs & Dosing

- Current data suggests class effect
- Dosing controversy
- Current guidelines still recommend target doses until more information is available

<i>Name</i>	<i>Initial Dose</i>	<i>Target Dose for Survival Benefit</i>
Captopril	6.25 mg TID	50 mg TID
Enalapril	2.5-5 mg twice daily	10 mg twice daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Ramipril	1.25-2.5 mg twice daily	5 mg twice daily
Quinapril	10 mg twice daily	20-40 mg twice daily
Fosinopril	5-10 mg daily	40 mg daily
Trandolapril	0.5-1 mg daily	4 mg daily

Adapted from Heart Failure in Pharmacotherapy: A Pathophysiologic Approach. Dipiro JT et al. 2005: pg 241

ACE-I Considerations

- Assess volume status
 - Prior to starting and increasing ACE-I
 - Hypotension
 - Elevated BUN/SrCr
 - BP & HR
- Remove other agents that \uparrow potassium
 - Potassium-sparing diuretics
 - Salt substitutes
 - Potassium supplements
- Monitoring
 - K⁺ SrCr BUN
 - BP, HR

Use of ARBs in HFrEF

- Major role
 - Consider as an alternative to ACE-I in pts w/ intolerance
 - Data is not as good with ARB
 - Other role: added to ACEI, BB, when aldosterone antagonists is not tolerated and pt is still symptomatic
- Combination therapy with ACE-I
 - Use as 4th agent in combo w/ ACE-I, β blockers, aldosterone inhibitors.
- Fallen out of favor d/t increased potassium

Drugs & Dose

<u>Drug Name</u>	<u>Initial Dose</u>	<u>Target Dose</u>
Candesartan *	4 - 8 mg daily	32 mg daily
Valsartan *	40 mg twice daily	160 mg twice daily
Losartan	12.5 - 25 mg daily	50 - 150 mg daily

*preferred agents

- Possible class effect
- Monitoring, contraindications, ADR same as ACEI (except cough)

Aldosterone Antagonists

- Starting to be used more often and sooner
- Recommend in NYHA II-IV
 - EF \leq 35%
 - After optimal doses β blockers, ACE-I, (and diuretics)
 - Of note, class II patients need CV hospitalization or high BMP
 - After acute MI with EF<40%
- Useful in patients needing additional antihypertensive agents

MOA

- Aldosterone receptor antagonist
- Decreases preload
 - Diuretic effect in distal tubule; K⁺ sparing
- Decreases afterload
 - Possible decrease of sympathetic activation
 - Increase arterial compliance
- Cardiac remodeling
 - Decrease myocardial and vascular fibrosis
- Decrease baroreceptor dysfunction
- Watch potassium!

Drugs & Dose

Spironolactone

- Studied in NYHA class III & IV
- Dose
 - Initiate at 12.5 mg to 25mg daily
 - Target of 25mg daily
- Anti-androgen effects

Eplerenone

- Studied in NYHA class II
 - CHF after MI
- Dose
 - Initiate at 25mg daily
 - Target of 50 mg once daily
- Benefits
 - More selective
 - Better tolerated

Hydralazine/Nitrates

- NYHA class III-IV HF \uparrow EF
 - In addition to optimal therapy with ACEI/ARB and beta-blockers (and AA)
- Use as an alternative to ACE-I and ARBs
 - Intolerant of ACE-I or ARB
 - Pts w/ severe renal dysfunction
 - Persistent hyperkalemia on ACE-I or ARB
- May improve mortality but not to the extent of ACE-I or ARBs
- *May play more of a role in African Americans*
 - *In addition to ACE-I*

“Feel Better” Medications

Diuretics

- Symptomatic relief of volume overload
- Can improve exercise tolerance
- Elimination of sodium and water results in a reduction of preload
- Furosemide is most commonly used; but bumentanide and torsemide have better oral bioavailability

Loop Diuretic Dosing

- Begin at low dose
 - Furosemide 20 to 40mg po q day
- Titrate to a loss of 1-2 lbs/day acutely, then tailor
- Self-adjusted diuretics for some pts
- Diuretic resistance: long-term use changes tubule or ion transport
 - ↑ dose or add thiazide to loop regimen
 - Loops have ceiling dose
 - Metolazone is most common thiazide

ADR & Monitoring

- Volume status
 - Overdiuresis: may cause acute renal failure / hypotension
 - Underdiuresis: worsening symptoms of volume overload
- Electrolyte Disturbances
- Chem panel
 - 3-5 days after starting regimen & changes in doses
- Inpatient vs. outpatient
- Response and compliance to regimen

Digoxin

- Used in HFrEF only, may worsen HFpEF
- Added to pts with persistent symptoms despite treatment with optimal doses of neurohormonal antagonists
 - Positive inotropic effects
 - Negative chronotropic effects
- The usual oral maintenance dose: 0.125 to 0.25 mg
- Females may not benefit and may have increased mortality

New Drugs in HFrEF

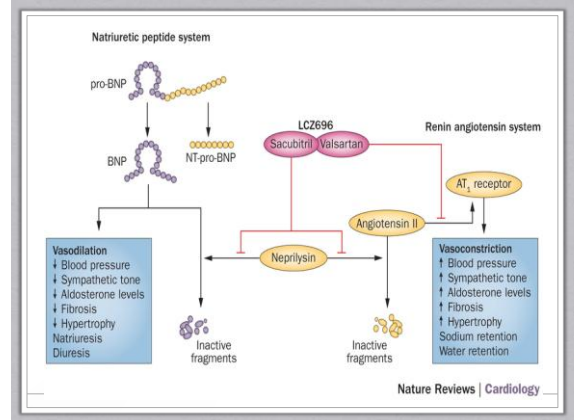
Approved 2015

Sacubitril / Valsartan (Entresto)

- Use
 - *2016 Update: *"In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE-I or ARB, replacement with an ARNI is recommended to further reduce morbidity and mortality."*
 - PARADIGM-HF: vs enalapril pts treated for 2 yrs
 - All-cause mortality NNT = 36
 - First hospitalization for worsening HF NNT=36
- Used in place of ACEI or ARB

MOA

- Blocks neprilysin, which is responsible for the breakdown of natriuretic peptides, bradykinin, adreomedullin, AND angiotensin II
 - Speculated that those with HF has increased levels of neprilysin
 - BNP levels are altered, therefore unreliable and not used in these patients
- ARB must be used in combination with neprilysin inhibitor to block increased RAAS levels



Dosing

Drug Name	Initial Dose	Target Dose
Sacubitril / Valsartan	49/51 mg twice daily for patients previously on ACEI or ARB	97 / 103* mg twice daily
	24/26 mg twice daily for ACEI / ARB naïve pts, eGFR <30, moderate liver impairment	

*103 mg is equivalent to 160mg BID of valsartan (different salts)
 **tablets are NOT proportionately the same (ie two 24/26 mg tablets ≠ 49/51 mg tablet)

- ***ARNI administered 36 hours after last dose of ACEI or ARB
- Dose should be increased every 2-4 weeks as tolerated

Additional Info

- Precautions/Contraindications
 - Angioedema
 - Contraindicated with those with history
 - Hypotension
 - Drugs that increase K+
- Adverse Effects
 - Hypotension
 - Hyperkalemia
 - Cough
 - Dizziness
 - Renal failure
 - Angioedema

More Additional Info...

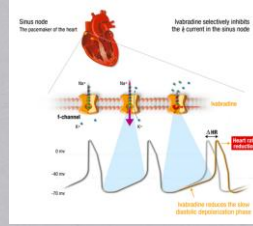
- Monitoring
 - K+ and renal function 1-2 weeks after initiation / dosage change
- Issues to consider
 - Cost: \$375 /month
 - Recommendation: continue use of standard HF therapy
 - Consider use if pt continues to have symptoms or recent exacerbation on optimized treatment

If Channel Inhibitor

- Ivabradine (Corlanor)
- Use
 - Reduce the risk of hospitalization in chronic HF with the following characteristics:
 - Stable, symptomatic heart failure
 - LVEF ≤35%
 - Sinus rhythm with resting HR ≥70 bpm
 - On maximum tolerated doses of BB or contraindication to BB therapy
- SHIFT and BEAUTIFUL trials

MOA

- Selectively binds to the If (funny current) channels in the SA node
 - Funny current because it is unusual in behavior
 - Accelerates diastolic depolarization in SA
- Ivabradine slows depolarization → slows SA activity → reduces HR
 - Does NOT alter myocardial contractility or intracardiac conduction
 - Does NOT affect other ion channels



Drug Name	Initial Dose	Max Dose
Ivabradine	5mg twice daily	10 mg twice daily

- If after 2 weeks and HR is > 60 bpm, increase to 10mg twice daily
 - HR < 50 bpm decrease to 2.5mg twice daily

ADR



- Adverse Effects
 - Bradycardia
 - Atrial fibrillation (d/c in this instance)
 - Phosphenes (visual brightness)
 - Sudden change in the brightness of light
 - Warn pts! Operate machinery with caution, esp at night
 - Most resolve in about 2 months

Additional Info

- Monitoring
 - Heart rate and rhythm
 - Dizziness and fatigue
 - Blood pressure
 - Vision changes
- Issues to consider
 - Cost: \$375 / month
 - Recommendation: continue use of standard HF therapy
 - Consider use if pt continues to have symptoms or HR > 70 bpm on optimized treatment
 - Consider use in pt intolerant of BB

Questions?