Pharmacotherapy in Chronic Heart Failure: Translating Evidence-Based Recommendations Into Practice

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Disclosures:

- I have no financial disclosures

Why Focus on Heart Failure (HF)?

- United States (US) prevalence estimated around 5,800,000[1]
- Leading cause of hospital admission for patients over 65[1]
  - 1,106,000 hospital discharges attributed to HF in 2006[1]
  - National 30-day readmission rate 24.7%[2]
- Associated with approx. 283,000 deaths/year[1]
- The estimated direct and indirect cost of HF in the US for 2010 is $39.2 billion[1]

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Causes of Heart Failure

- Ischemic Heart Disease
- Hypertension
- Idiopathic Cardiomyopathy
- Infections
  - Viral / Bacterial myocarditis
  - Chagas disease (parasitic disease common in Central America)
- Toxins
  - Alcohol or cytotoxic drugs
- Valvular Disease
- Prolonged Arrhythmias
- Endocrine Disorders
- Peripartum CM

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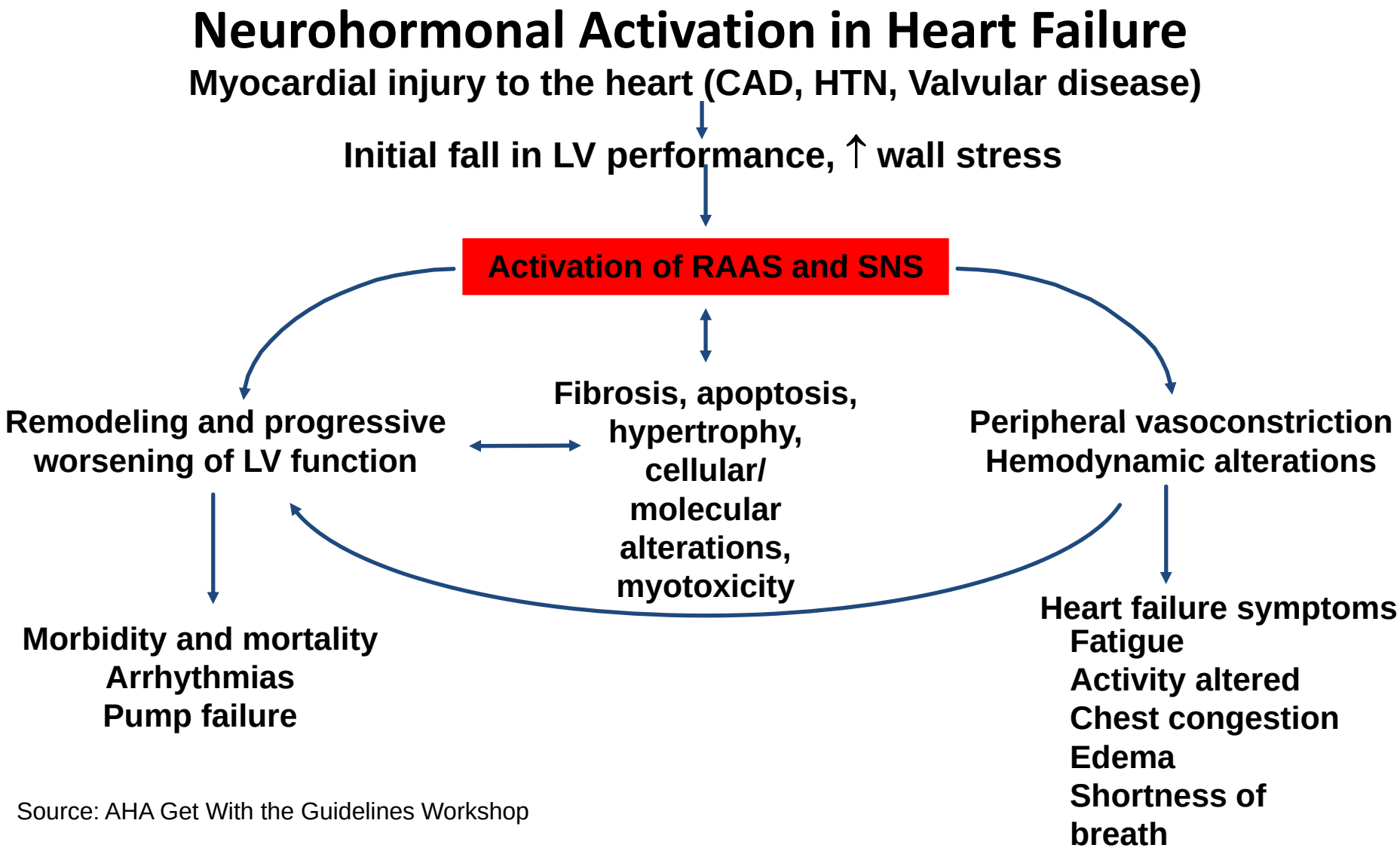
HF as a Progressive Model

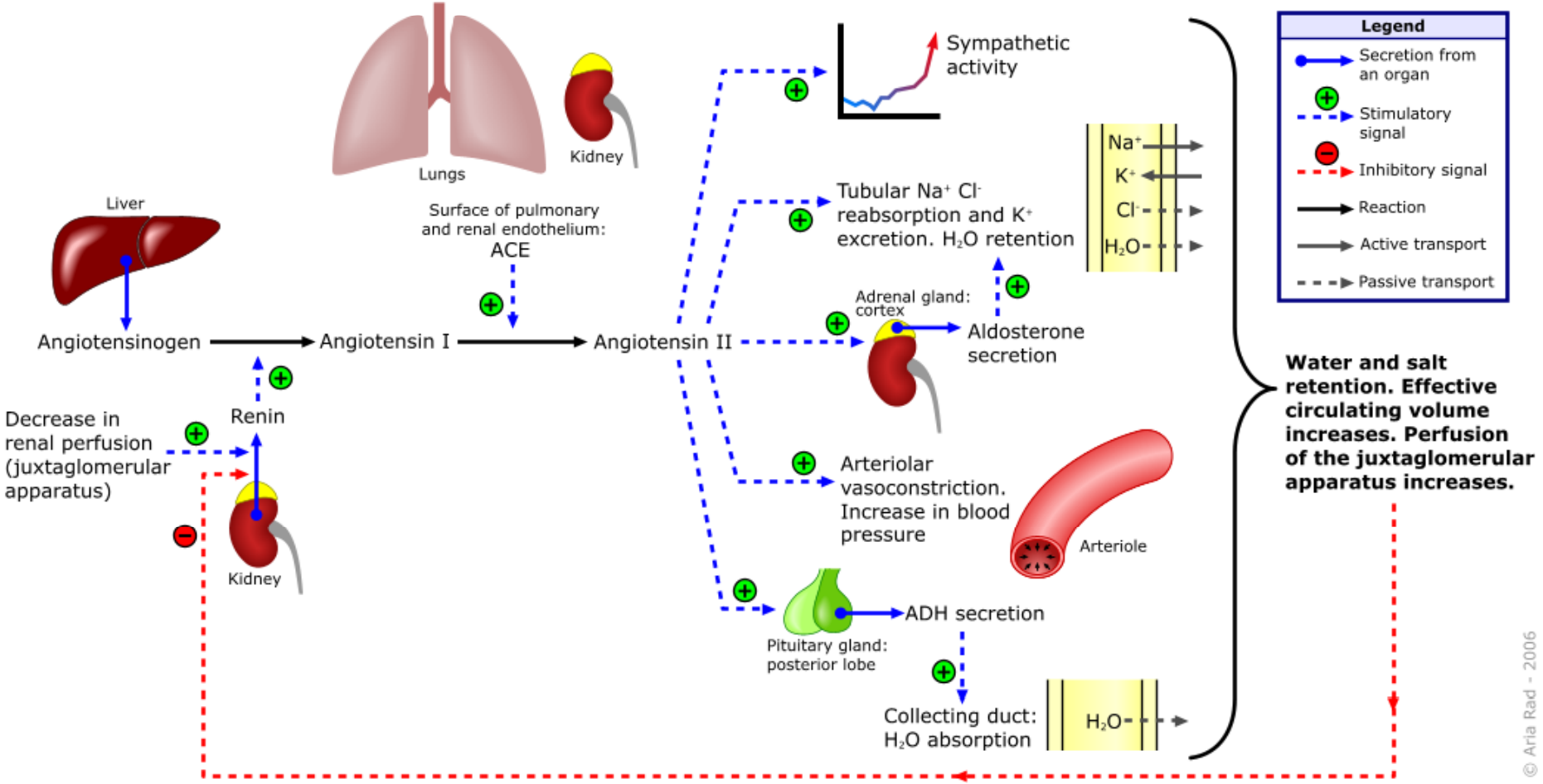
- HF is a complex clinical syndrome that impairs the ability of the ventricle to fill with or eject blood[3]
- HF is a constellation of symptoms produced by a complex circulatory and neurohormonal response to cardiac dysfunction
  - Sympathetic nervous system (SNS)
  - Renin- Angiotensin- Aldosterone system (RAAS)

Neurohormonal Activation in Heart Failure



Source: AHA Get With the Guidelines Workshop

Renin-angiotensin-aldosterone system



Source: Wikipedia Commons

Ventricular Remodeling and Its Prevention

- The chambers of the heart have the capacity to alter (remodel) their size and configuration in response to acute and chronic changes
- Activation of the RAAS and stimulation of SNS contribute to the process
- Remodeling results in physical changes in the ventricle, impacting its ability to pump and/or fill effectively
- **The goal of HF therapy is to minimize and possibly reverse the areas of remodeling in order to preserve ventricular function**

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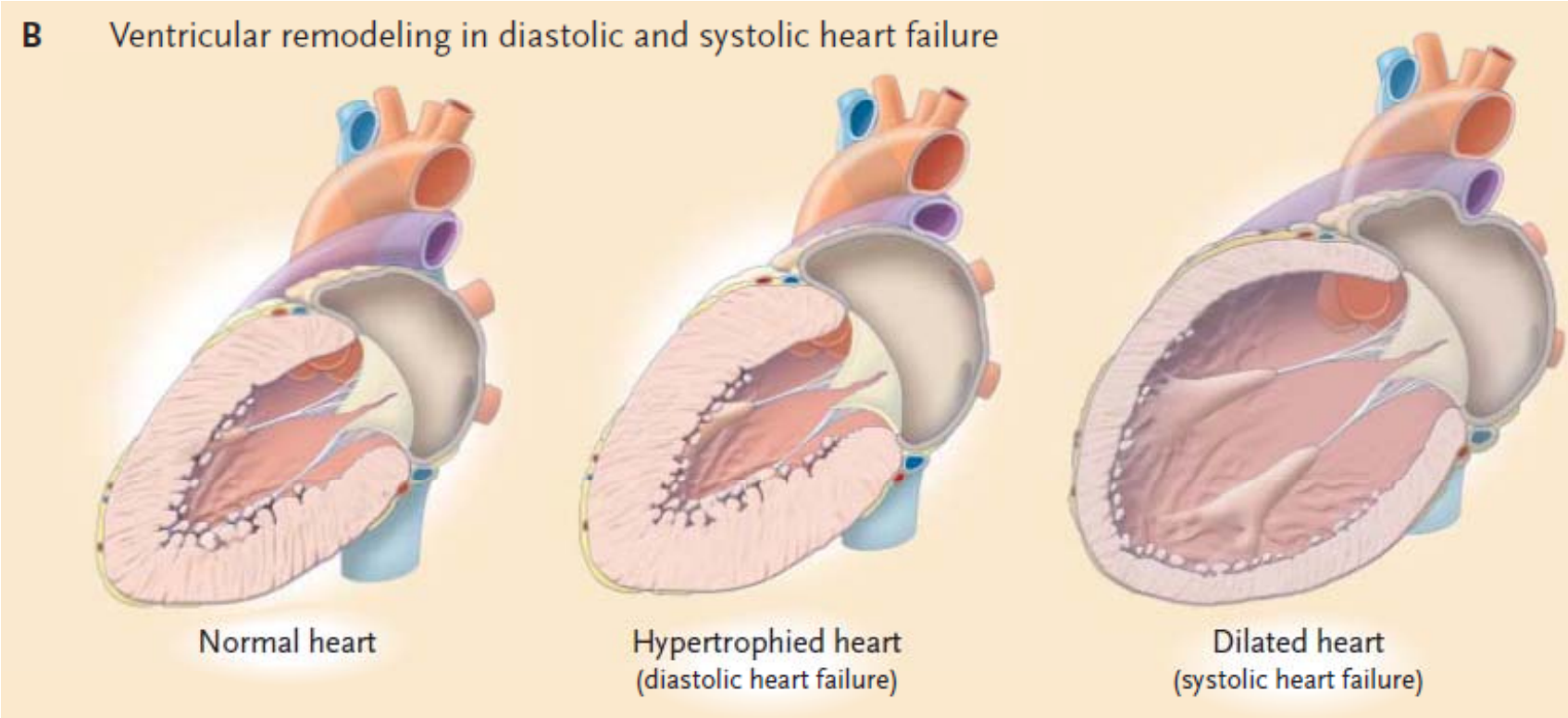
Ventricular Remodeling



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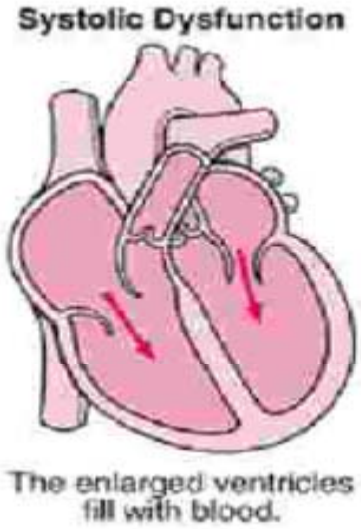
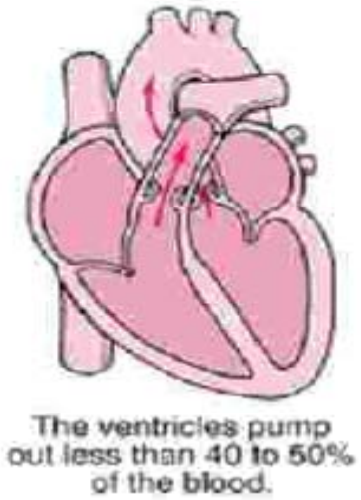
Systolic Dysfunction

- Inability of the left ventricle to effectively ***pump*** blood to the body

- Weakened muscle, enlarged heart size, inability of heart to empty

- The ejection fraction in systolic dysfunction is **less than 40%**





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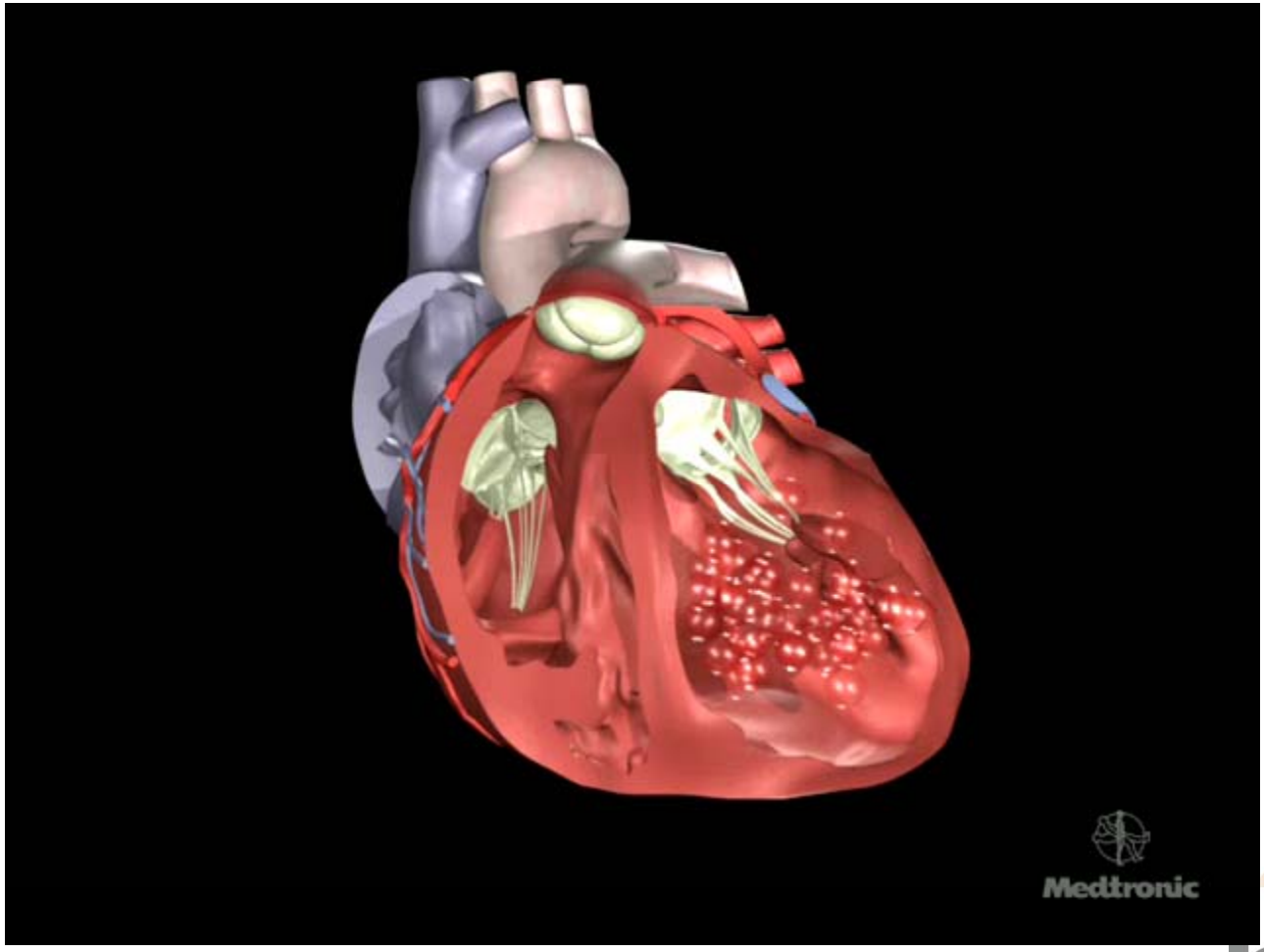
Systolic Dysfunction



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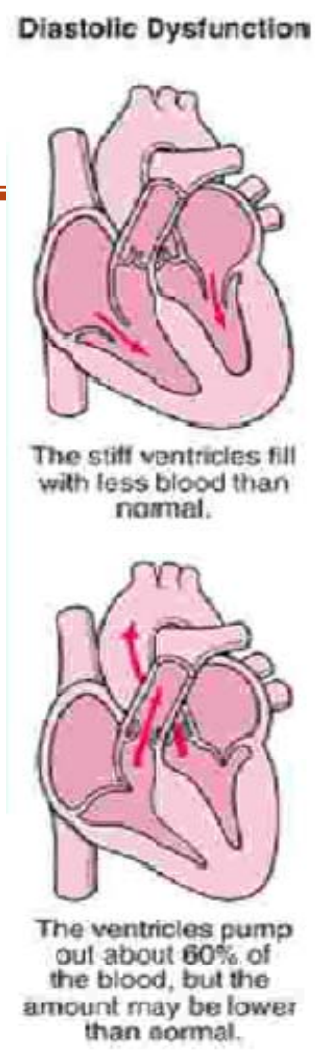
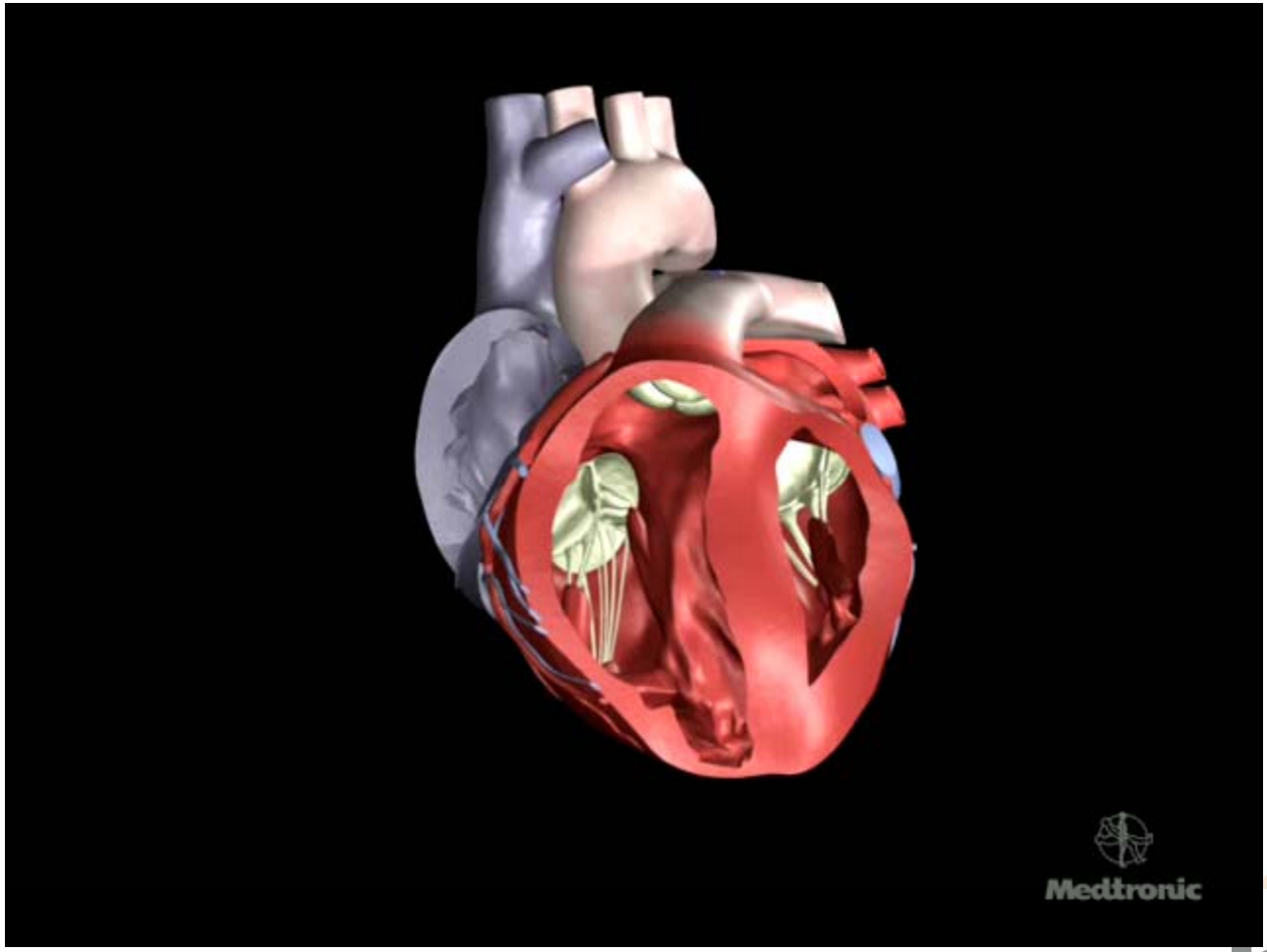
Diastolic Dysfunction

(Preserved Systolic Function)

- Myocardial relaxation is abnormal
- The left ventricle is unable to ***fill*** because of the inability to ***relax***
- The EF may be normal (>50%)
- Concomitant systolic and diastolic dysfunction usually co-exist



Diastolic Dysfunction



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Clinical Manifestations of Heart Failure

Symptoms from Biventricular Failure

- Fatigue/weakness
- Dyspnea
- Decreased exercise tolerance
- Inability to concentrate
- Loss of appetite
- Feels cold

Symptoms from LV Impairment

- Fatigue/ weakness
- Dyspnea
- Orthopnea
- PND
- Sudden orthopnea that awakens from sleep

Symptoms from RV Impairment

- Fatigue/ weakness
- Bilateral leg swelling
- Abdominal bloating
- Abdominal pain (right)
- Weight gain
- Loss of appetite

Hunt SA et al. *Circulation*. 2001;104:2996-3007.
Cohn NJ et al. *Hurst's The Heart*. 8th ed. New York: McGraw-Hill; 1994:557-571.

Evaluation of the HF Patient

Three fundamental questions must be addressed:

1. Is the LVEF preserved or reduced?
2. Is the structure of the LV normal or abnormal?
3. Are there other structural abnormalities such as valvular, pericardial, or right ventricular abnormalities that could account for the clinical presentation?

Stages of Heart Failure

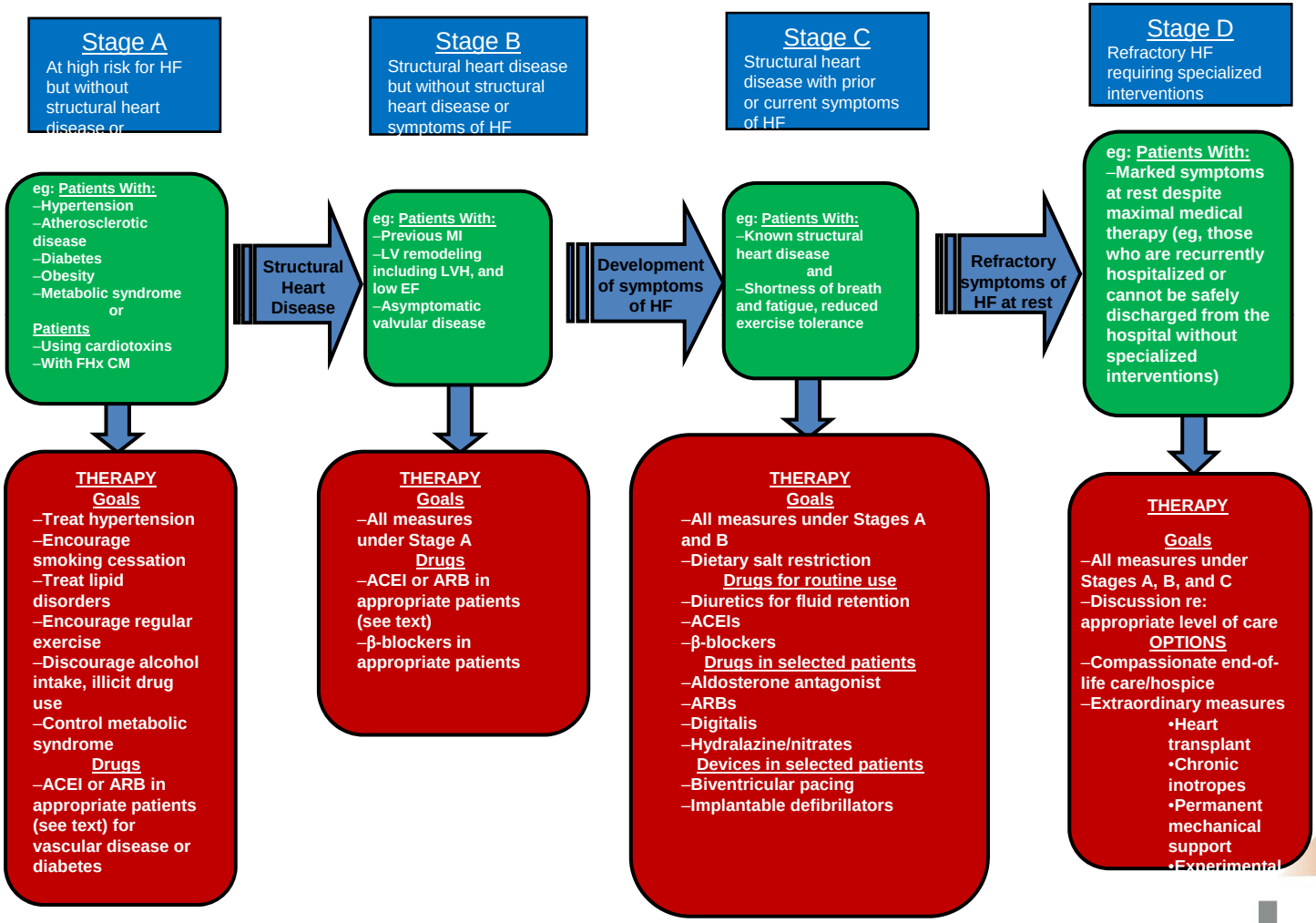

Table reproduced from ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

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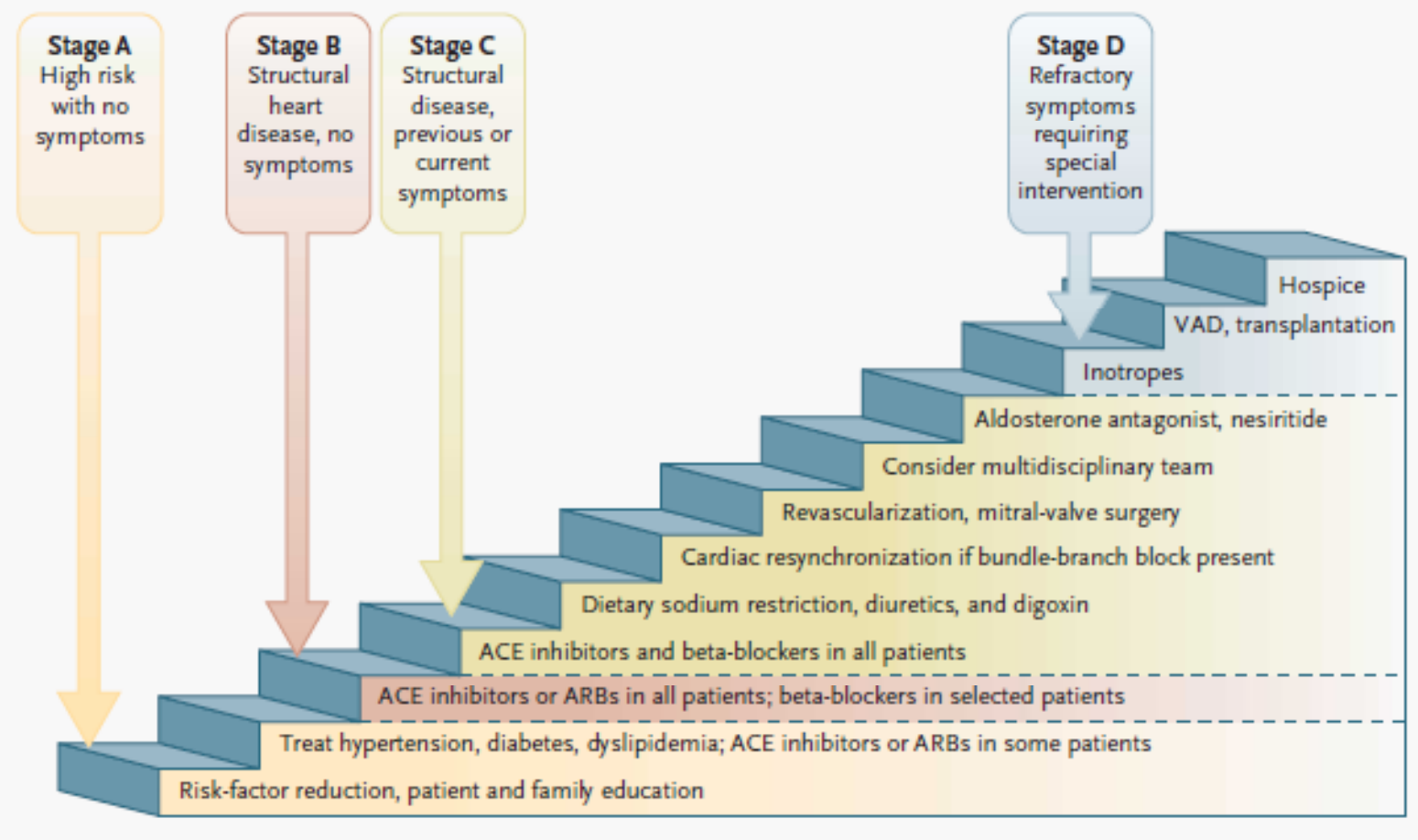
NYHA Functional Class

Class		Patient Description
Class I	Asymptomatic	• No limitation of physical activity • Ordinary physical activity does not cause fatigue, palpitation, or dyspnea
Class II	Symptomatic with moderate exertion	• Slight limitation of physical activity • Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III	Symptomatic with minimal exertion	• Marked limitation of physical activity • Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
Class IV	Symptomatic at rest	• Unable to carry out any physical activity without discomfort • Symptoms include cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

New York Heart Association/Little Brown and Company, 1964. Adapted from: Farrell et al. *JAMA*. 2002;287:890-897.

Stages of HF and Treatment Options



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AHA/ACC, HFSA Guideline Documents

- **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults:**
  - http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192064
- **HFSA 2010 Comprehensive Heart Failure Practice Guidelines:**
  - http://download.journals.elsevierhealth.com/pdfs/journals/1071-9164/PIIS1071916410001739.pdf

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Applying Classification of Recommendations and Level of Evidence

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk Procedure/ Treatment **SHOULD** be performed/ administered	*Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	*Benefit ≥ Risk* *Additional studies with broad objectives needed; Additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	*Risk ≥ Benefit* *No additional studies needed* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**

Level of Evidence:

Level A:	Data derived from multiple randomized clinical trials or meta-analyses Multiple populations evaluated
Level B:	Data derived from a single randomized trial or nonrandomized studies Limited populations evaluated
Level C:	Only consensus of experts opinion, case studies, or standard of care Very limited populations evaluated

Medication Management in Chronic HF

- Angiotensin Converting Enzyme Inhibitors: ACE-I
- Angiotensin Receptor Blockers: ARBs
- Beta Blockers
- Aldosterone Antagonists
- Hydralazine / Nitrates
- Diuretics
- Cardiac Glycosides

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Angiotensin Converting Enzyme Inhibitors: ACE-I

- ACE-I block the conversion of angiotensin I to angiotensin II
  - A substance in the blood that causes vasoconstriction and raises blood pressure
- **Recommended for all HF patients with reduced LVEF[3]**
- **ACE-I have been shown to[3]:**
  - **Relieve symptoms**
  - **Stabilize/ reverse LV remodeling**
  - **Reduce the risk of death**
  - **Reduce hospitalization**

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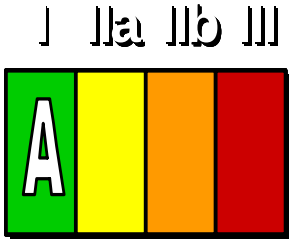
ACE-I



ACE-I are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated [3]

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
ACE-inhibitors				
Captopril	Capoten	6.25 mg tid	50 mg tid	122.7 mg/day[160]
Enalapril	Vasotec	2.5 mg bid	10 mg bid	16.6 mg/day[42]
Fosinopril	Monopril	5-10 mg qd	80 mg qd	n/a
Lisinopril	Zestril, Prinivil	2.5-5 mg qd	20 mg qd	*4.5 mg/day (low dose ATLAS) 33.2 mg/day (high dose ATLAS)[161]
Quinapril	Accupril	5 mg bid	80 mg qd	n/a
Ramipril	Altace	1.25-2.5 mg qd	10 mg qd	n/a
Trandolapril	Mavik	1 mg qd	4 mg qd	n/a

Table reproduced from HFSA 2010 Comprehensive Heart Failure Practice Guidelines

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Prescribing Tips: ACE-I

- Contraindications: Renal failure, renal artery stenosis, angioedema, pregnancy, ↑K+ (>5.5 mmol/L), ↓BP[3]
- Titration to goal dose is usually achieved by doubling the dose every week as tolerated[4]
- B/P, renal function, and K+ levels should be checked 1-2 weeks after initiation
- Abrupt withdrawal should be avoided
- S/E: Cough, angioedema, ↓BP, ↑K+

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Angiotensin Receptor Blockers: ARBs

- May be prescribed as an **alternative** to ACE-I

- ARBs directly block the effects of angiotensin II on the angiotensin receptors in the tissues

- **ARBs have been shown to[3]:**
  - **Relieve symptoms**
  - **Stabilize/ reverse LV remodeling**
  - **Reduce the risk of death**
  - **Reduce hospitalization**

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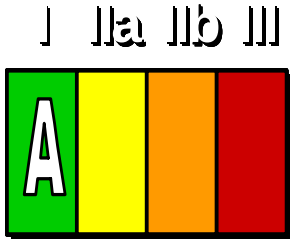
ARBs



ARBs are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE- inhibitor intolerant[3]

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Angiotensin Receptor Blockers				
Candesartan	Atacand	4-8 mg qd	32 mg qd	24 mg/day[162]
Losartan	Cozaar	12.5-25 mg qd	150 mg qd	129 mg/day[163]
Valsartan	Diovan	40 mg bid	160 mg bid	254 mg/day[164]

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Prescribing Tips: ARBs

- Contraindications: Renal failure, renal artery stenosis, angioedema, pregnancy, ↑K+ (>5.5 mmol/L), ↓BP[3]
- Titration to goal dose is usually achieved by doubling the dose every 2 weeks as tolerated[4]
- B/P, renal function, and K+ levels should be checked 1-2 weeks after initiation
- S/E: angioedema, renal impairment, BP, ↑K+

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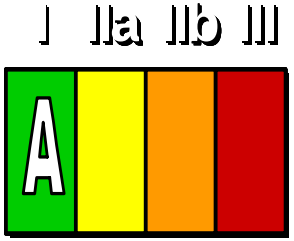
Beta Blockers

- Cardioprotective effects due to *blockade* of excessive SNS stimulation
- Slows the heart rate making each contraction more efficient and decreases the heart's oxygen demand
- Benefits of beta blockers NOT a "class effect"
  - Three beta blockers have been shown to reduce mortality in chronic HF
    - Bisoprolol, metoprolol succinate (sustained release)= $beta_1$, blockade
    - Carvedilol= $beta_1$, $beta_2$ and $alpha_1$ blockade
- When given in concert with ACE-I certain beta-blockers help HF patients relieve symptoms, stabilize / reverse LV remodeling, reduce the risk of death, and reduce hospitalization

Beta Blockers



Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated[5]

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Beta-blockers				
Bisoprolol	Zebeta	1.25 mg qd	10 mg qd	8.6 mg/day[47]
Carvedilol	Coreg	3.125 mg bid	25 mg bid	37 mg/day[165]
Carvedilol	Coreg CR	10 mg qd	80 mg qd	
Metoprolol succinate CR/XL	Toprol XL	12.5-25 mg qd	200 mg qd	159 mg/day[48]

Table reproduced from HFSA 2010 Comprehensive Heart Failure Practice Guidelines

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Prescribing Tips: Beta Blockers

- Contraindications: Acute HF, ↓BP, ↓HR, aortic stenosis, sick sinus syndrome, asthma
- Fluid volume status should be optimized before starting beta blockers
- Initiate at a low dose
- Titration to goal dose is usually achieved by increasing dose every 2 weeks as tolerated[4]
- Monitor closely for fluid retention, B/P and HR
- Avoid abrupt discontinuation

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Aldosterone Antagonists

- Activation of aldosterone appears to play a role in HF pathophysiology
- Aldosterone antagonists reduced the progression of HF in **select patients** (EF < 35%, NYHA class III and IV)
  - Examples: Spironolactone, eplerenone
- **Aldosterone antagonists have been shown to[3]:**
  - **Relieve symptoms, improve functional class**
  - **Reduce the risk of death**
  - **Reduce hospitalization**

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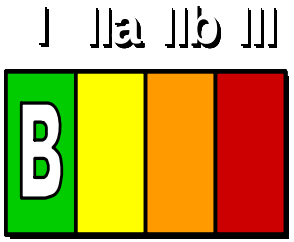
Aldosterone Antagonists



Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine 2.5 mg/dL or less in men or 2.0 mg/dL or less in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists[3]

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Aldosterone Antagonists				
Spironolactone	Aldactone	12.5 to 25 mg qd	25 mg qd	26 mg/day[60]
Eplerenone	Inspra	25 mg qd	50 mg qd	42.6 mg/day[61]

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Prescribing Tips: Aldosterone Antagonists

- Contraindications: Renal dysfunction
  Creatinine ≥ 2.5 mg/dL in men or ≥ 2.0 mg/dL in women, K+ ≥ 5.0 mEq/L
- Initiate at a low dose
- Renal function and K+ levels should be checked at 3 days, 1 week, and monthly after initiation[4]
- S/E: renal failure, ↑K+, gynecomastia

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Hydralazine / Isosorbide Dinitrate

- Hydralazine
  - Arterial Vasodilator
  - Little effect on venous tone and cardiac filling pressure
- Isosorbide Dinitrate
  - Venous vasodilator
- Combination therapy achieves both arterial and venous vasodilatation
- **Hydralazine / Isosorbide Dinitrate has been shown to[3]:**
  - **Reduce the risk of death**
  - **Significant outcome benefit in the African American population**

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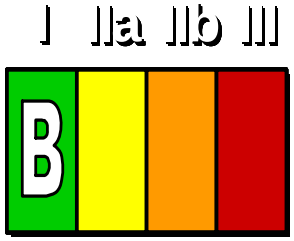
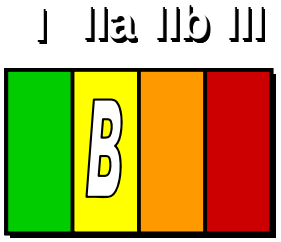
Recommendations for Hydralazine and Nitrates



The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, beta blockers, and diuretics[5]



The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta blocker for symptomatic HF and who have persistent symptoms[3]

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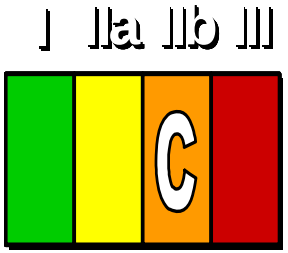
Recommendations for Hydralazine and Nitrates



A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency[3]

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
Fixed dose Hydralazine/ Isosorbide dinitrate	BiDil	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate tid	142.5 mg hydralazine/76 mg isosorbide dinitrate/day[166]
Hydralazine	Apresoline	37.5 mg qid	75 mg qid	270 mg/day[167]
Isosorbide dinitrate	Isordil	20 mg qid	40 mg qid	136 mg/day[167]

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Prescribing Tips: Hydralazine and Nitrates

- Contraindications: Nitrate sensitivity
- S/E: Headache, dizziness, ↓BP, orthostatic hypotension, syncope

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Diuretics

- Key therapy in symptom management
- Act on the kidneys to relieve fluid retention
- Reduces pulmonary and peripheral fluid accumulation
- Dose titrated in response to daily weight / symptoms
- Electrolyte abnormalities, volume depletion, and renal impairment are possible complications
- Should never be used alone to treat heart failure

Diuretic Recommendations

Table 4. Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg*	2 to 3 days
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic		

mg indicates milligrams; IV, intravenous.
*Higher doses may occasionally be used with close monitoring.

Table reproduced from ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

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Cardiac Glycosides

- Inhibits Na^+- K^+- ATPase pump in cell membranes
  - Enhances contraction of cardiac muscle
- Reduces activation of SNS
- Controlled trials have shown long-term digoxin therapy:
  - Reduces symptoms
  - Increases exercise tolerance
  - Reduces hospitalization rates for decompensated HF
  - Does not improve survival

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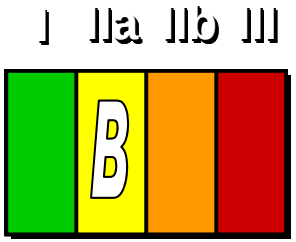
Benefits of Digitalis



Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF[3]

Prescribing Tips: Digitalis

- Contraindications: AV block, bradycardia, ↑K+, renal failure
- Narrow therapeutic serum level
  - Should be < 1.0 ng/ml[4]
- S/E: AV blocks, bradycardia, ventricular arrhythmias, visual disturbances

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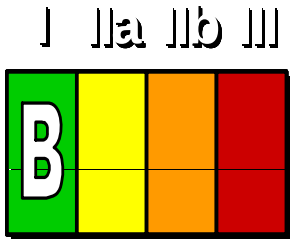
Medications to Avoid in HF

- **NSAIDS, COX-2 inhibitors**
  - risk of renal failure and fluid volume retention
- **Calcium Channel Blockers**
  - Verapamil, diltiazem (negative inotropic effects)
- **Antiarrhythmic agents**
  - All class I agents and sotolol (class III) Calcium Channel Blockers



Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible[3]

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Hoag's Heart Failure Team

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  - Medical Director
- Jennifer Ballard-Hernandez, NP, AACC
  - Nurse Practitioner, Program Manager
- Vanessa Schultz, NP
  - Nurse Practitioner
- Cathie Rassp, RN
  - HF Nurse

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Thank You

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