Chronic Heart Failure Pharmacotherapy

PHAR 452

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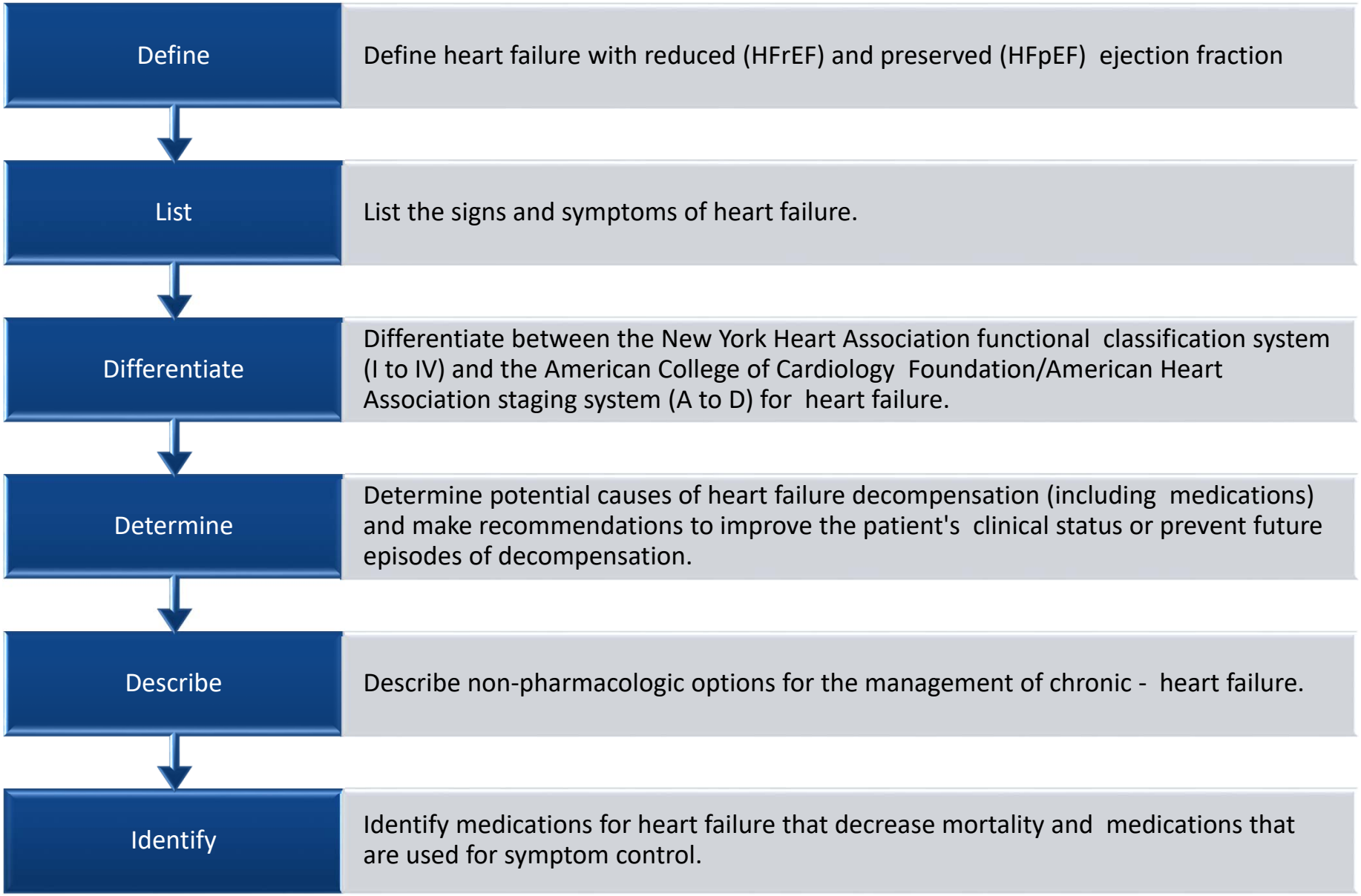
Reading:

- Parker, Robert B., et al.. "Chronic Heart Failure." Pharmacotherapy: A Pathophysiologic Approach, 10e Eds. Joseph T. DiPiro, et al. New York, NY: McGraw-Hill,

Learning Objectives



Learning Objectives

Identify	• Identify medications that should be utilized in each stage (A to D) of the American College of Cardiology Foundation/American Heart Association staging system.
Discuss	• Discuss appropriate patient selection, initiation, dosage titration, and monitoring for the following heart failure therapies: angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and aldosterone antagonists.
Differentiate	• Differentiate between the role of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and the combination of hydralazine and nitrate therapy in the treatment of heart failure
Describe	• Describe the role of diuretics and digoxin in the treatment of heart failure, and make recommendations regarding appropriate use and monitoring
Differentiate	• Differentiate between the treatment of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Heart Failure

Progressive clinical syndrome

Heart is incapable of meeting the metabolic needs of the body

- Can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with blood or eject blood
  - Any disorder damaging the pericardium, heart valves, myocardium, or ventricle function

Chronic heart failure

- Reduced or preserved ejection fraction

Acute decompensated heart failure (ADHF)

Epidemiology

- Lifetime risk: 20%
- Mortality rate: 50% within 5 years of diagnosis
- 1 in 9 deaths mentioned HF in the death certificate
- An estimated 650,000 new diagnoses occur every year
- Annual hospitalizations: > 1 million
- 30-day readmission rate: 23%
- the most common hospital discharge diagnosis in individuals over age 6
- Annual total cost of care: > $30 billion

Etiology

Results from any disorder which affects the ability of the heart to contract or relax

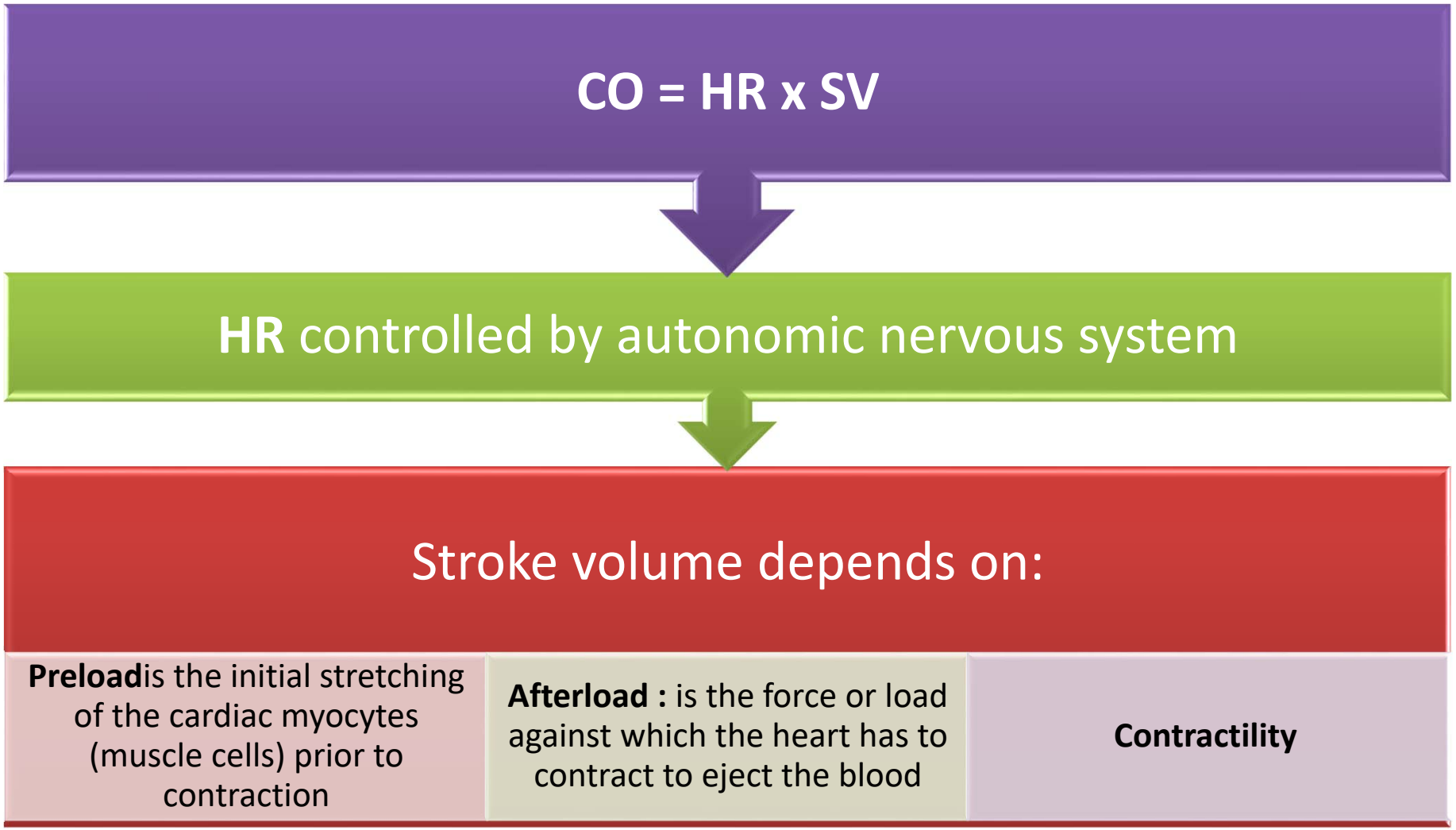
Systolic dysfunction (Contraction)

- **Reduction in muscle mass (MI)**
- Dilated cardiomyopathies
- Ventricular hypertrophy
  - Pressure overload
  - Volume overload

Diastolic dysfunction (relaxation)

- **Increased ventricular stiffness**
- Ventricular hypertrophy
  - Infiltrative myocardial disease
  - Myocardial ischemia
  - Mitral or tricuspid valve stenosis
- Pericardial disease

Heart Failure Pathophysiology



Pathophysiology – Normal Function

Preload

- Ability of heart to alter force of contraction is dependent on preload → increased stretch = increased force of contraction

Afterload

- Sum of forces preventing active forward ejection of blood by the ventricle
  - Ejection impedance
  - Wall tension
  - Regional Wall geometry
- Estimated by systemic vascular resistance (SVR)
- Inverse relationship between afterload and stroke volume
  - Increasing afterload = decreased stroke volume

Neuorohormonal Model

HF is systemic disease and progression is mediated mostly by neurohormones

- neurohormonal activation
- **norepinephrine, angiotensin II, aldosterone**

Explains disease progression

Medication targets to **slow progression: neurohormonal blockade**

Neurohormones

Angiotensin II

- Vasoconstriction and sodium retention
- Increased norepinephrine
- Increased aldosterone
- Increased arginine vasopressin release
- Ventricular hypertrophy and remodeling

Norepinephrine

- Tachycardia
- Vasoconstriction
- Increased contractility
- Increased risk of arrhythmia
- Ventricular hypertrophy and remodeling

Aldosterone

- Causes Na^+ retention (and K+ wasting)
- May produce interstitial cardiac fibrosis
- May increase risk of arrhythmias

Other neurohormones

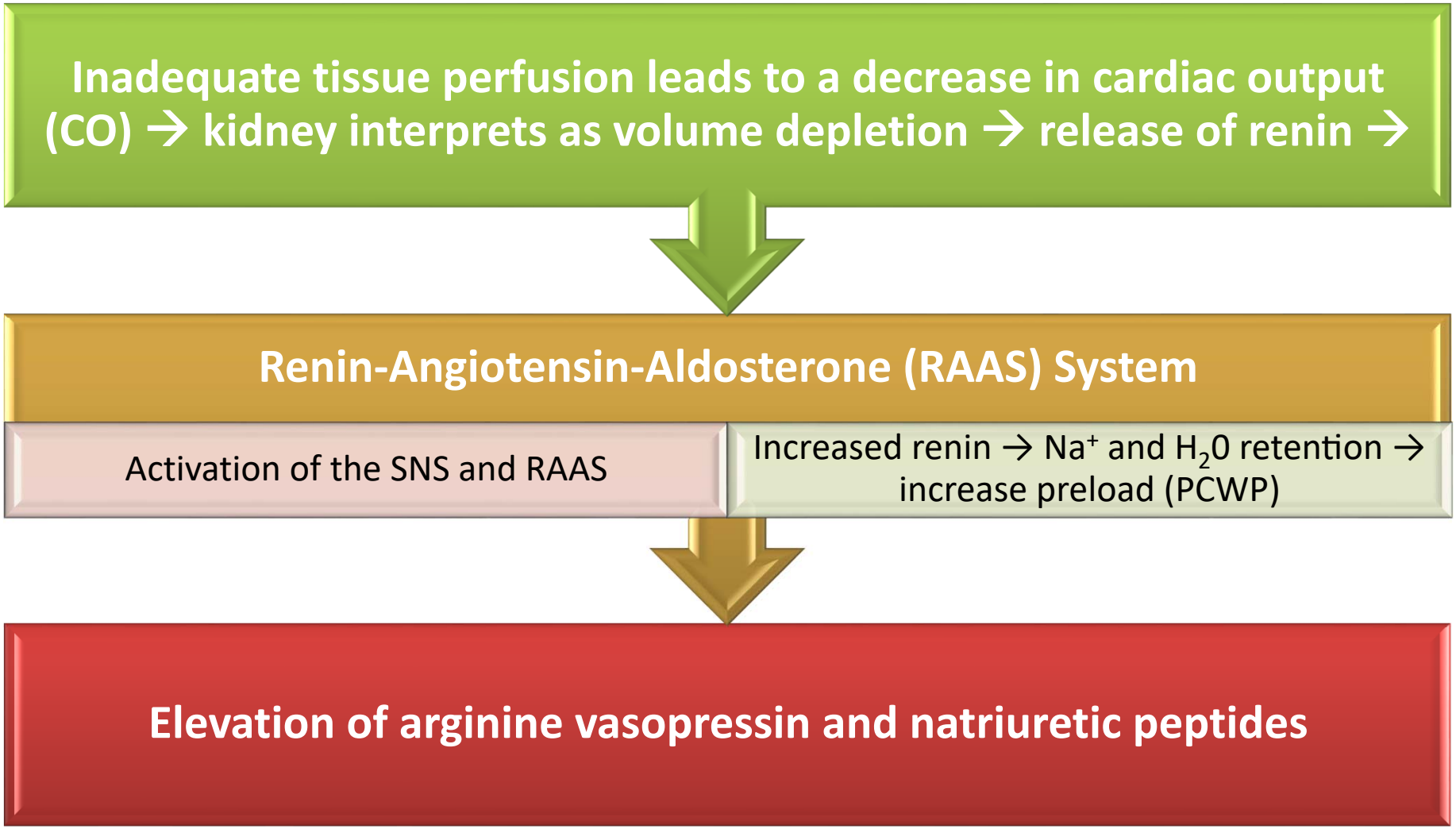
Natriuretic peptides (BNP)

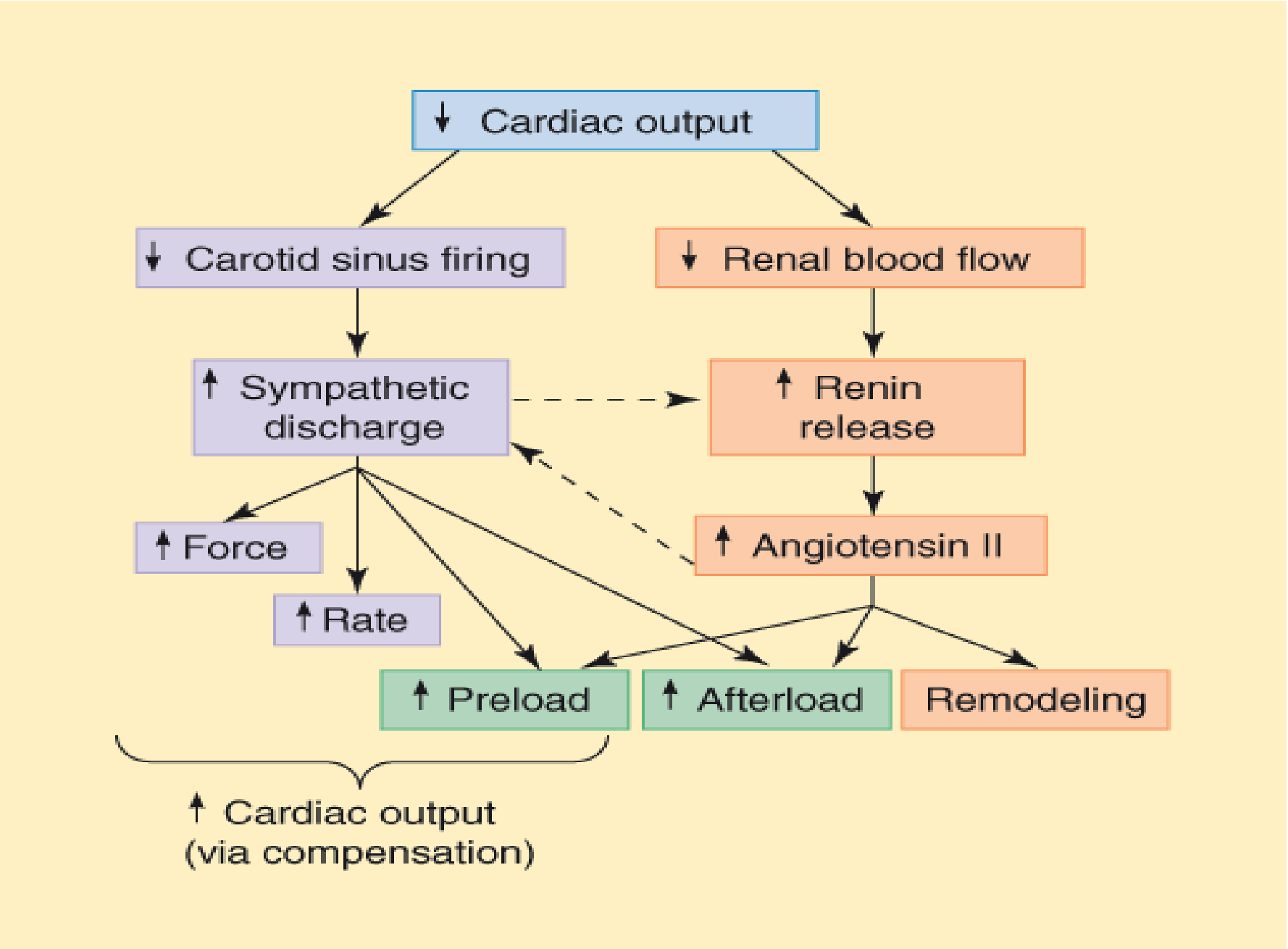
- Released in response to pressure (stretch) or volume overload
  - Increased diuresis and natriuresis
  - Activation of RAAS and SNS
- Plasma levels are good diagnostic markers

Arginine Vasopressin (AVP)

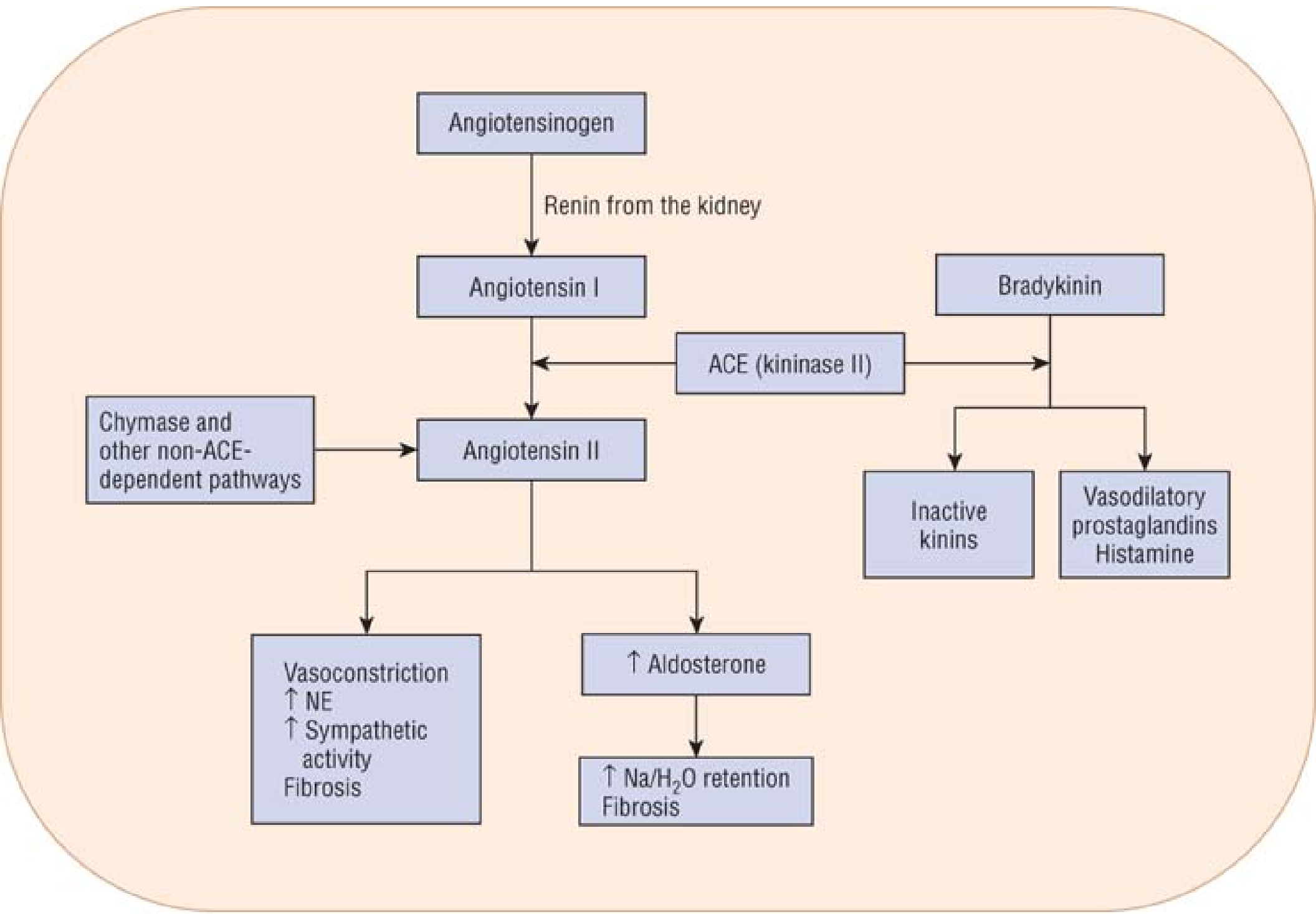
- Regulates renal water excretion and plasma osmolality
- Released in response to volume depletion
  - Increased free water reabsorption → may lead to volume overload and hyponatremia
  - Increased arterial vasoconstriction → may lead to reduced CO
  - Other maladaptive response → May cause remodeling by cardiac hypertrophy

Neurohormonal, Renal, and Vascular Adjustments





Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com



Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic Approach, 10th Edition, www.accesspharmacy.com

Heart Failure Pharmacotherapy

01

Decrease preload

02

Decrease afterload

03

Increase contractility

04

Block neurohormonal activation

Ejection Fraction (EF)

Fraction of blood pumped with each heartbeat

Calculated from echocardiogram

Ratio: stroke volume/end-diastolic volume

Stroke volume: volume of blood ejected during systole

End-diastolic volume: volume of blood in ventricle at end of diastole

Normal range: ~ 55 – 70%

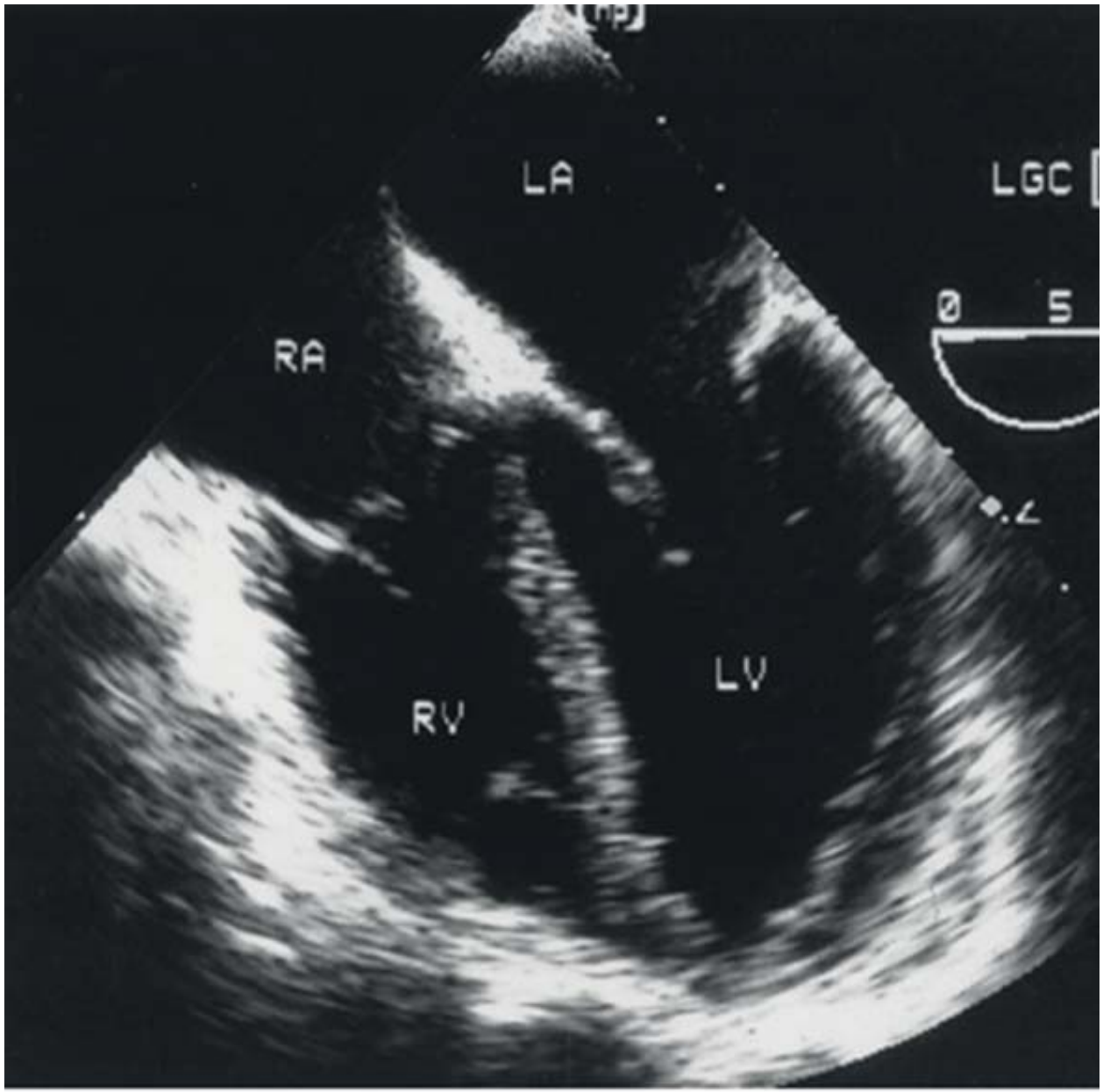
Echocardiogram

Uses sound waves to visualize structure

Useful for:

Estimating left ventricular ejection fraction (EF), grading of diastolic dyfunction	Examining ventricle size, valve function, and wall motion abnormalities

Echocardiogram



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson
P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

Echocardiogram

Transthoracic echocardiogram (TTE)	• Transducer on chest wall
Transesophageal echocardiogram (TEE)	• Transducer in esophagus

HFrEF

Reduced ejection fraction (EF ≤ 40%)

Impaired wall motion, dilated ventricle, **decreased contractility during systole**

Causes

- Majority: coronary artery disease (~70%)
  - Ischemic cardiomyopathy
- Non-ischemic cardiomyopathy
  - Hypertension
  - Valvular disease
  - Thyroid disease (hyperthyroidism)
  - Cardiotoxins (alcohol, some chemotherapy)
  - Myocarditis (viral infections)
  - Idiopathic

HFpEF

Preserved ejection fraction (EF ≥ 50%)

- ~50% patients with heart failure

Impaired ventricle relaxation and filling during diastole

- Stage I, II, III
- Ventricle unable to accept adequate volume of blood
- Ventricle does not fill at low pressure or is unable to maintain normal SV

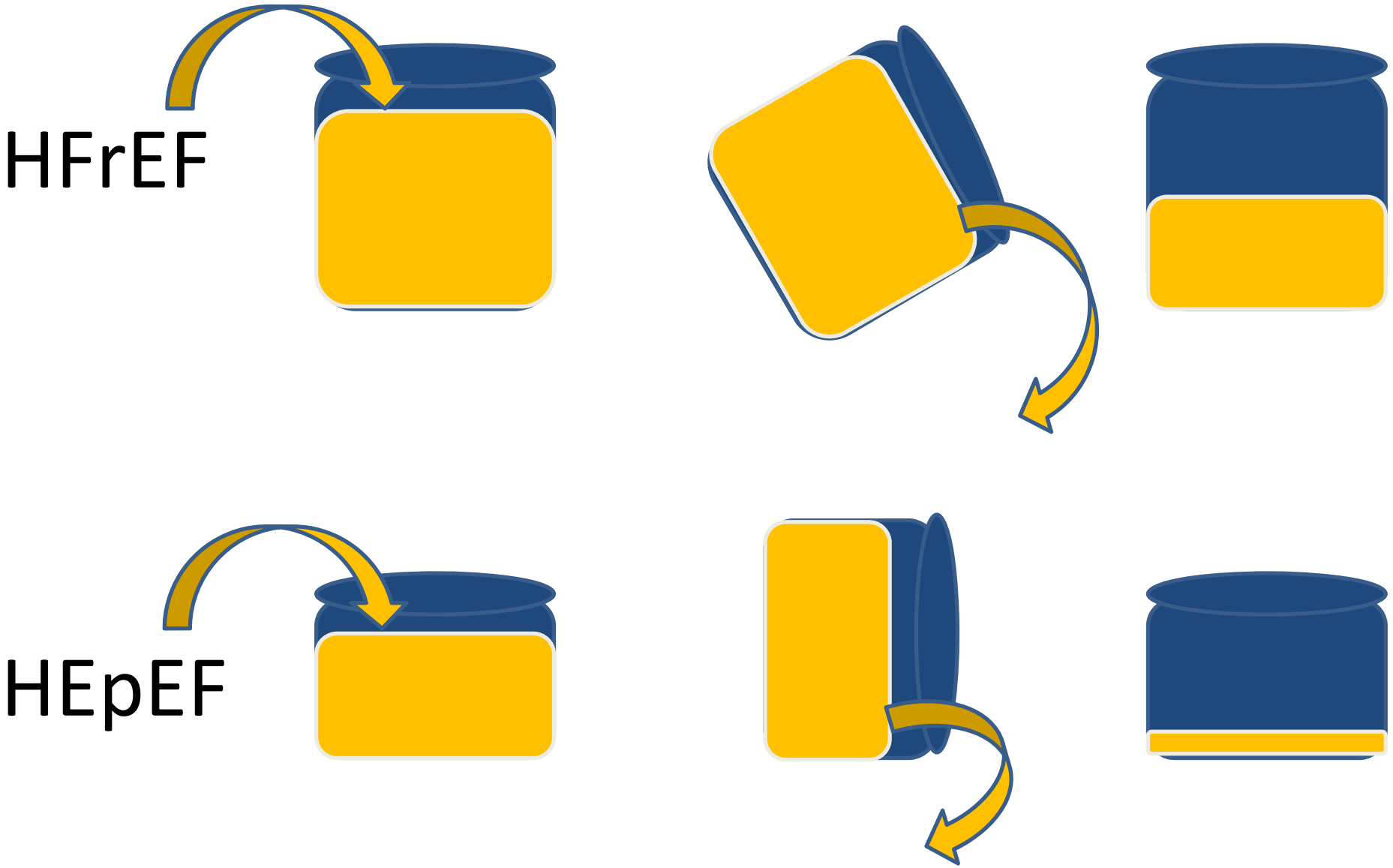
Causes

- Majority: decreased elasticity and increased ventricular stiffness
  - Hypertension
  - Age-related changes
- Various cardiomyopathies
  - Restrictive, infiltrative, hypertrophic

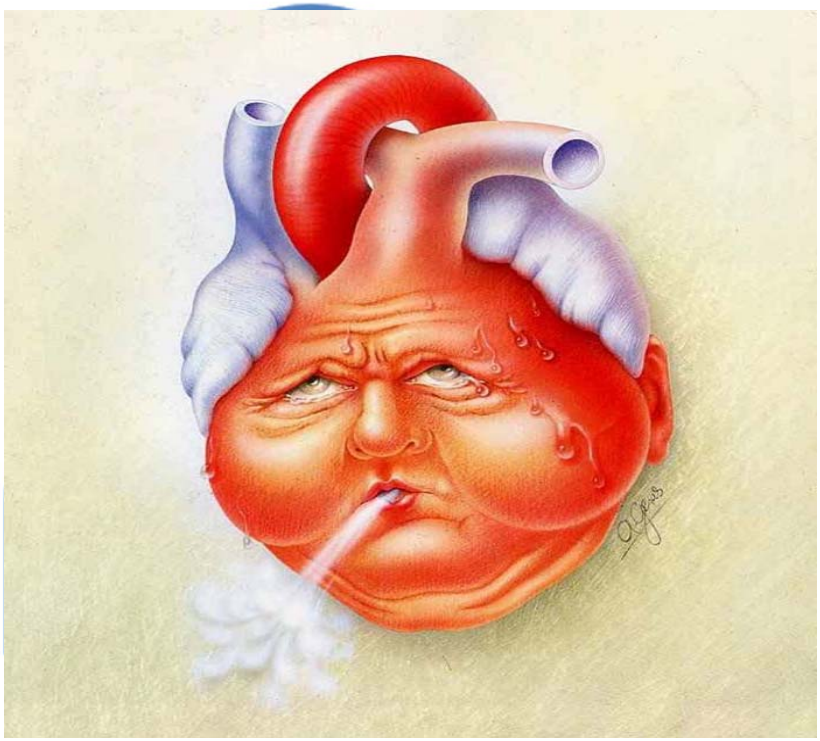
Normal Heart Function

(Left Ventricle)

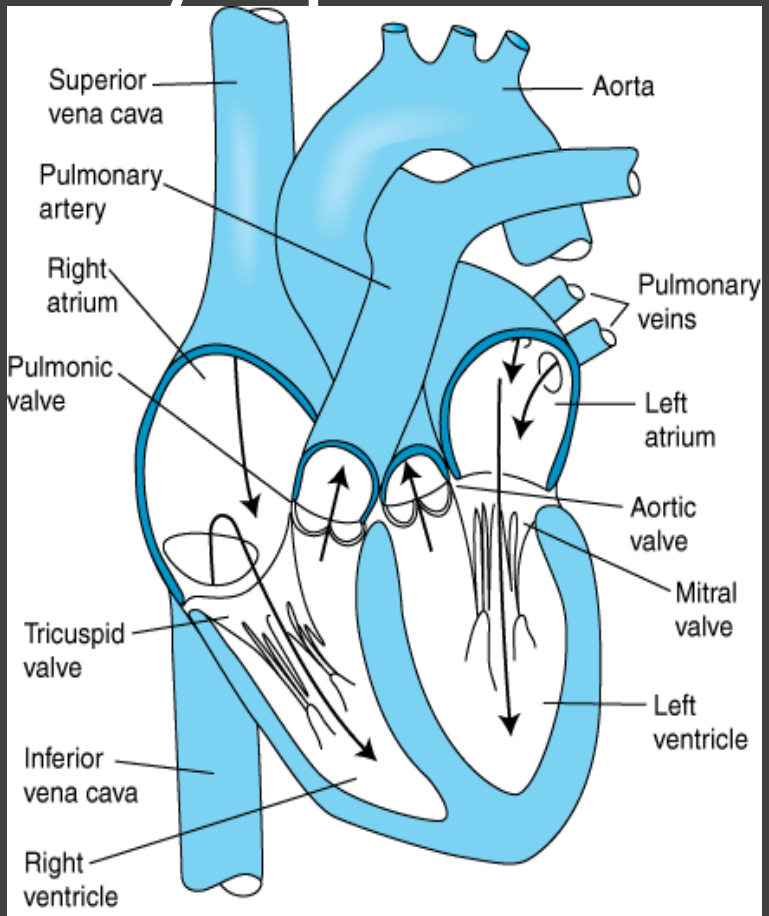
HFrEF versus HFpEF



Clinical Presentation and Patient Evaluation



Signs and Symptoms



Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology, 7th Edition*: http://www.accessmedicine.com

Dyspnea, fatigue, exercise intolerance, fluid overload and weight gain

Congestion occurs behind the failing ventricle(s)

Left ventricle: pulmonary congestion	Right ventricle: systemic congestion

Signs and Symptoms

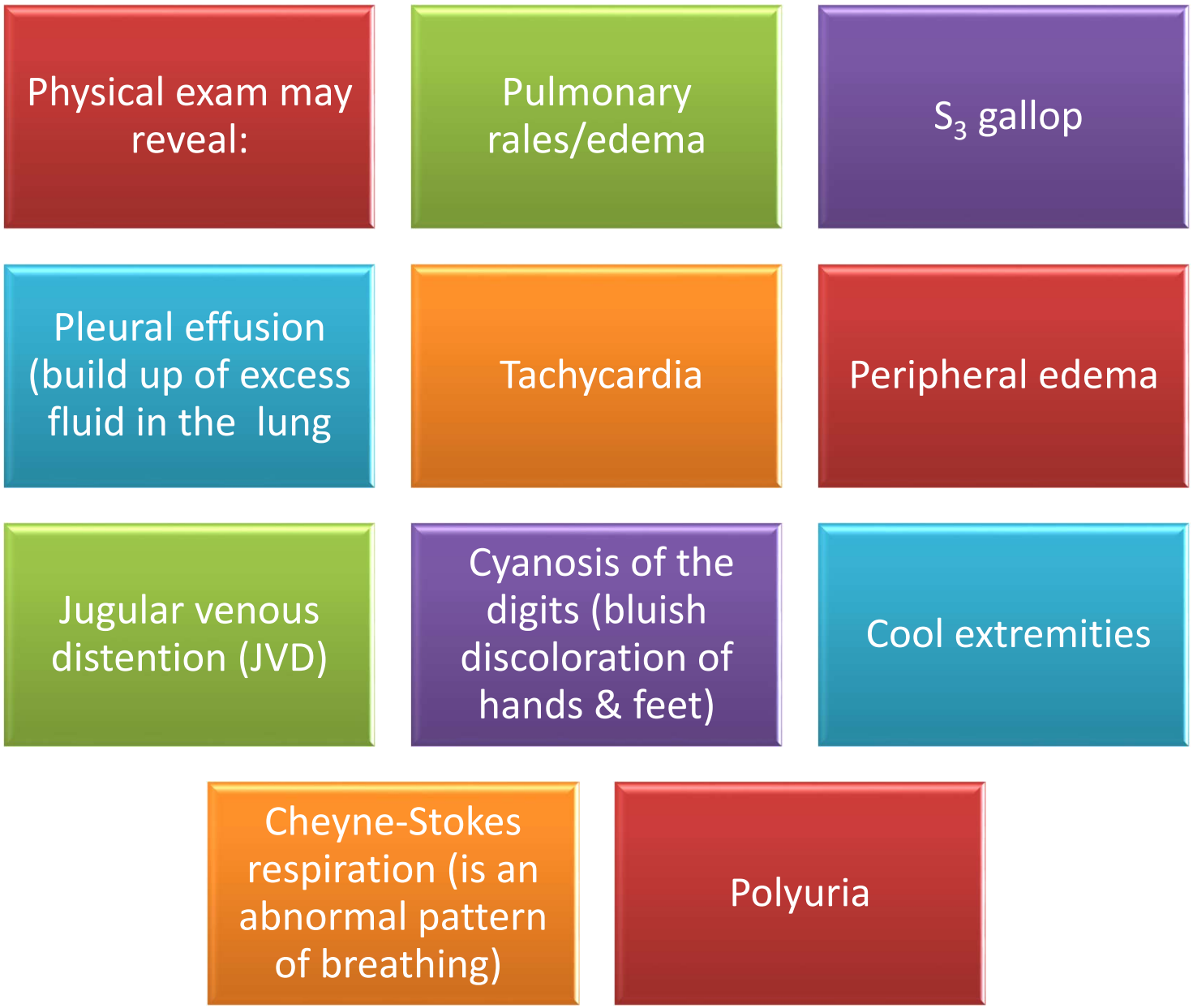
Left ventricle: **pulmonary congestion**

- **Symptoms:** dyspnea, orthopnea, paroxysmal nocturnal dyspnea, tachypnea, cough
- **Signs:** pulmonary rales, pulmonary edema

Right ventricle: **systemic congestion**

- **Symptoms:** abdominal pain , anorexia, nausea, bloating, poor appetite, early satiety, ascites (buildup of fluid in the abdomen)
- **Signs:** peripheral edema, jugular venous distension, hepatojugular reflux, hepatomegaly
- Can effect medication absorption and metabolism

Clinical Presentation & diagnosis s signs



Signs Associated with Symptoms

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Clinical Feature	Symptoms	Signs
Congestion	Dyspnea, orthopnea PND, fatigue, anorexia	LEE, ascites, hepatomegaly, anasarca, ↑JVD pulmonary edema, cachexia
Severe congestion	Severe dyspnea at rest	Crackles, rales, effusion, tachypneic, tachycardia
Poor perfusion	Confusion, weakness, cold periphery	Pallor, Low SBP, anuria or oliguria

Jugular Venous Distention

Source: Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine, 3rd Edition:* http://www.accessmedicine.com

Clinical Presentation & Diagnosis Labs

BNP > 100 pg/mL (Neurohormones secreted from myocardium in response to increases in myocardial stretch)

EKG- LV hypertrophy, myocardial ischemia, arrhythmias

SCr, serum Na, CBC

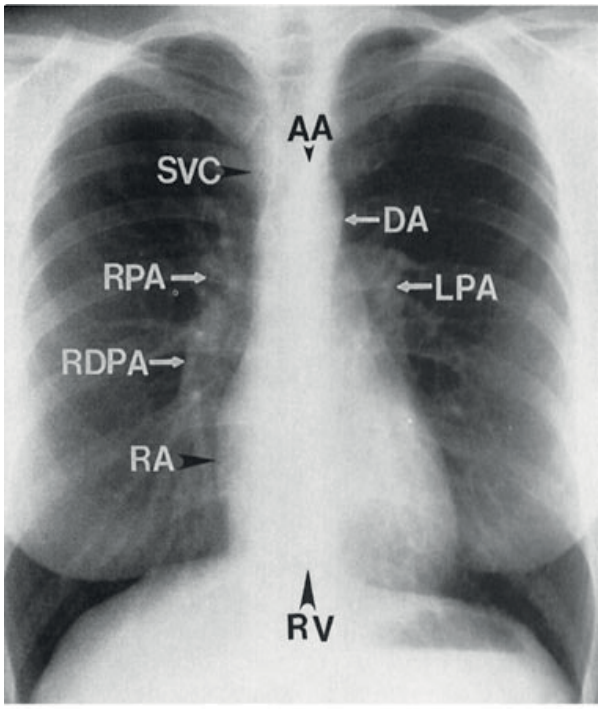
CXR

Echocardiogram- the single most useful test

– Valves, LVH, LVEF, structure abnormalities

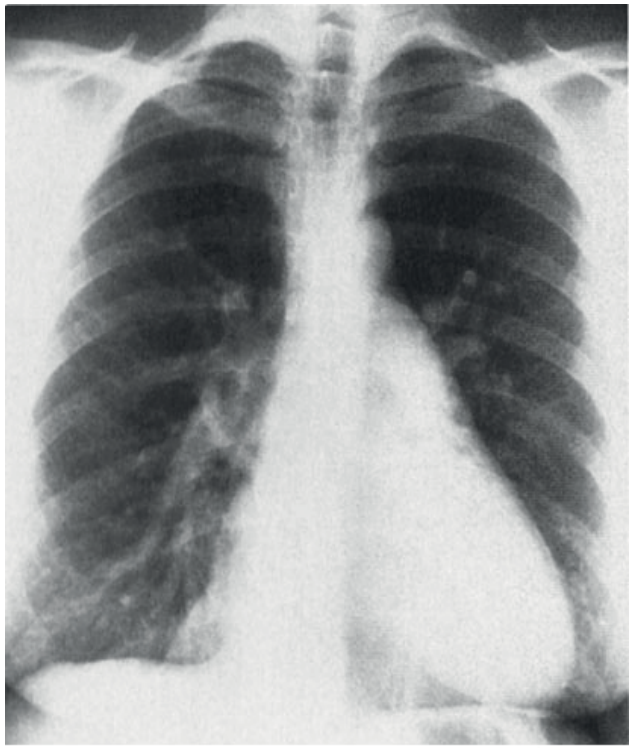
Any other labs to assess for any co-morbidities/risk factors, i.e. lipid panel, angiogram, A1C, etc.

Chest X Ray

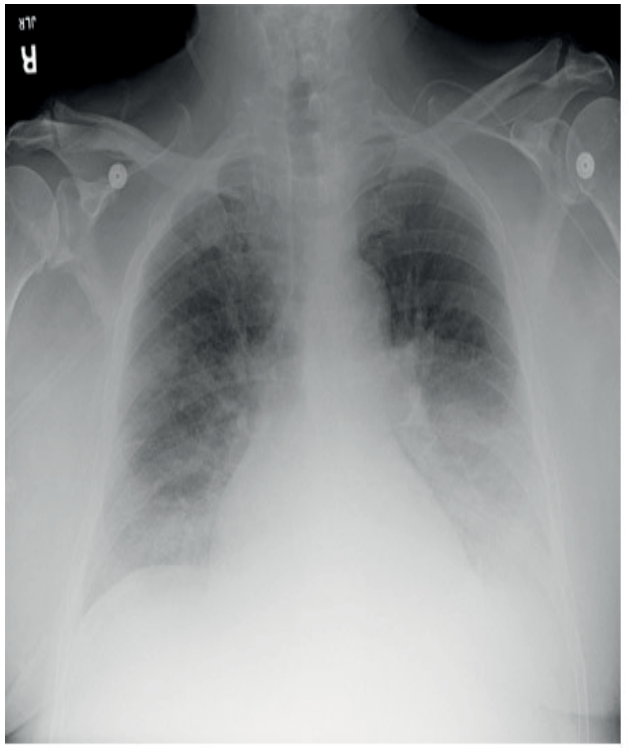


A

Normal



Cardiomegaly



Pulmonary Edema

Natriuretic Peptide Monitoring

Neurohormones secreted from myocardium in response to increases in myocardial stretch (increases in ventricular volume and pressure)

Aid in differential diagnosis of dyspnea; interpret in context of clinical picture

BNP (B-type natriuretic peptide)

- BNP **< 100 pg/mL**: HF unlikely
- BNP **100 – 500 pg/mL**: consider HF and other potential causes
- BNP **> 500 pg/mL**: **HF very likely**

Natriuretic Peptide Monitoring

Monitoring recommendations for chronic heart failure ambulatory patients

Monitoring is used to:

- Support diagnosis of heart failure (especially if uncertain)
- Establish prognosis and disease severity
- Achieve optimal drug therapy dosing
  - BNP levels improve with treatment
  - lack of improvement = increased risk of mortality or hospitalization

From: 2017 ACCF/AHA Guideline for the Management of Heart Failure

Classification and Staging of HF

New York Heart Association (NYHA) Functional Classification

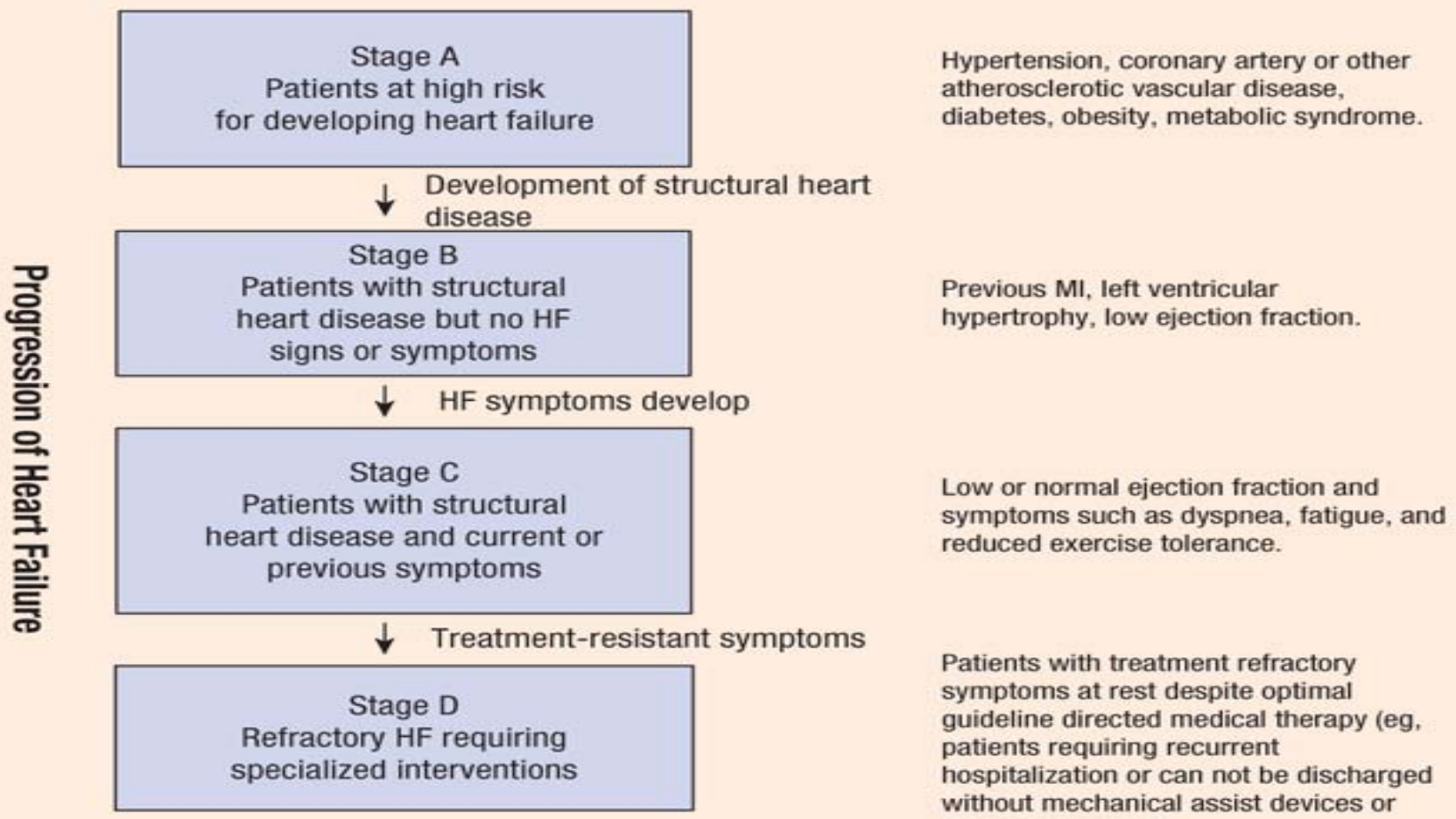
I – **No limitations** in physical activity due to HF symptoms Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.

II - **Ordinary physical activity** will cause HF symptoms (slight limitation) Ordinary physical activity results in fatigue, palpitation, dyspnea.

III - **Less-than-ordinary activity** will cause HF symptoms (marked limitation) Although patients are comfortable at rest, less than ordinary activity will lead to symptoms

IV – HF symptoms are **present at rest** Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

ACCF/AHA Heart Failure Staging



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Citation: Chronic Heart Failure, DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. *Pharmacotherapy: A Pathophysiologic Approach, 10e;* 2017. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146056207 Accessed: February 27, 2020

NYHA Vs. ACC/AHA

NYHA is a functional classification- based on ability to function with minimal restriction- subjective

Pts can move back and forth between NYHA stages

ACC/AHA staging complements NYHA

Pts cannot move back in ACC/AHA stages

Both systems together enable clinicians to better assess risk factors, management, and prognosis

ACCF/AHA vs NYHA Classifications

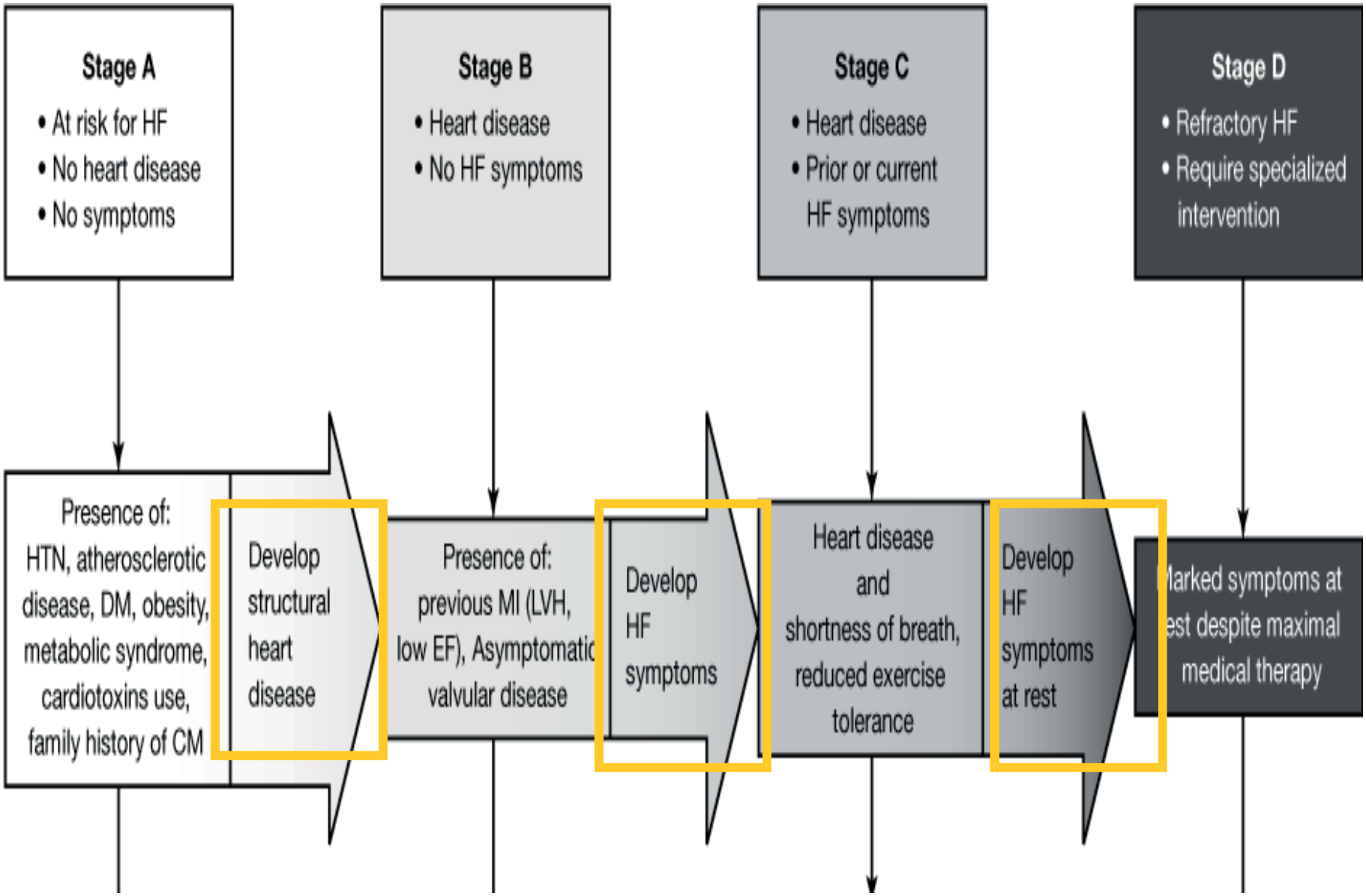
Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications

ACCF/AHA Stages of HF[38]		NYHA Functional Classification[46]	
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	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

At Risk For Heart Failure

Heart Failure



HR Exacerbation Factors

Noncompliance with medications or diet

- Food high in sodium content

Cardiac events

- ischemia, infarction, atrial fibrillation

Medications

- negative inotropic effects
- cardiotoxic
- sodium and water retention

Drugs That Can Induce or Exacerbate HF

Negative ionotropic effect

- **Antiarrhythmics, calcium channel blockers, itraconazole**

Cardiotoxic drugs

- **Doxorubicin, epirubicin, daunomycin, cyclophosphamide, trastuzumab, bevacizumab, mitoxantrone, ifosfamide, lapatinib, sunitinib, imatinib, ethanol, amphetamines (cocaine, MDMA)**

Sodium and water retention

- **NSAIDS, COX-2 inhibitors, TZDs, glucocorticoids, androgens/estrogens, high dose salicylates**

Unknown mechanism

- **Infliximab, etanercept, dronedarone**

Goals of Therapy

Improve quality of life

Relieve or reduce symptoms

Prevent or minimize hospitalizations for exacerbations of heart failure

Slow progression of disease process

Decrease mortality, prolong survival

non-pharmacologic options for the management of chronic heart failure.

Non-Pharmacologic Treatment

Improve cardiovascular risk factors

Patient education:

- activity level, diet, discharge medications, follow-up appointments, self-monitoring of symptoms and weight

Exercise training program or regular physical activity

Non-Pharmacologic Treatment

Sodium restriction

- Reasonable for patients with symptomatic HF
- AHA: < 1.5 grams/day
  - 2017 HF Guidelines: use AHA restriction for Stages A and B
- Insufficient data for stage C and D
  - 2017 HF Guidelines: consider some restriction (< 3 grams/day?)
  - Clinical practice: usually 2 grams/day

Fluid restriction to 2 L/day if:

- Hyponatremia (serum Na <130 mEq/L)
- Persistent or recurrent fluid retention despite high diuretic doses and sodium restriction

From: 2017 ACCF/AHA Guideline for the Management of Heart Failure

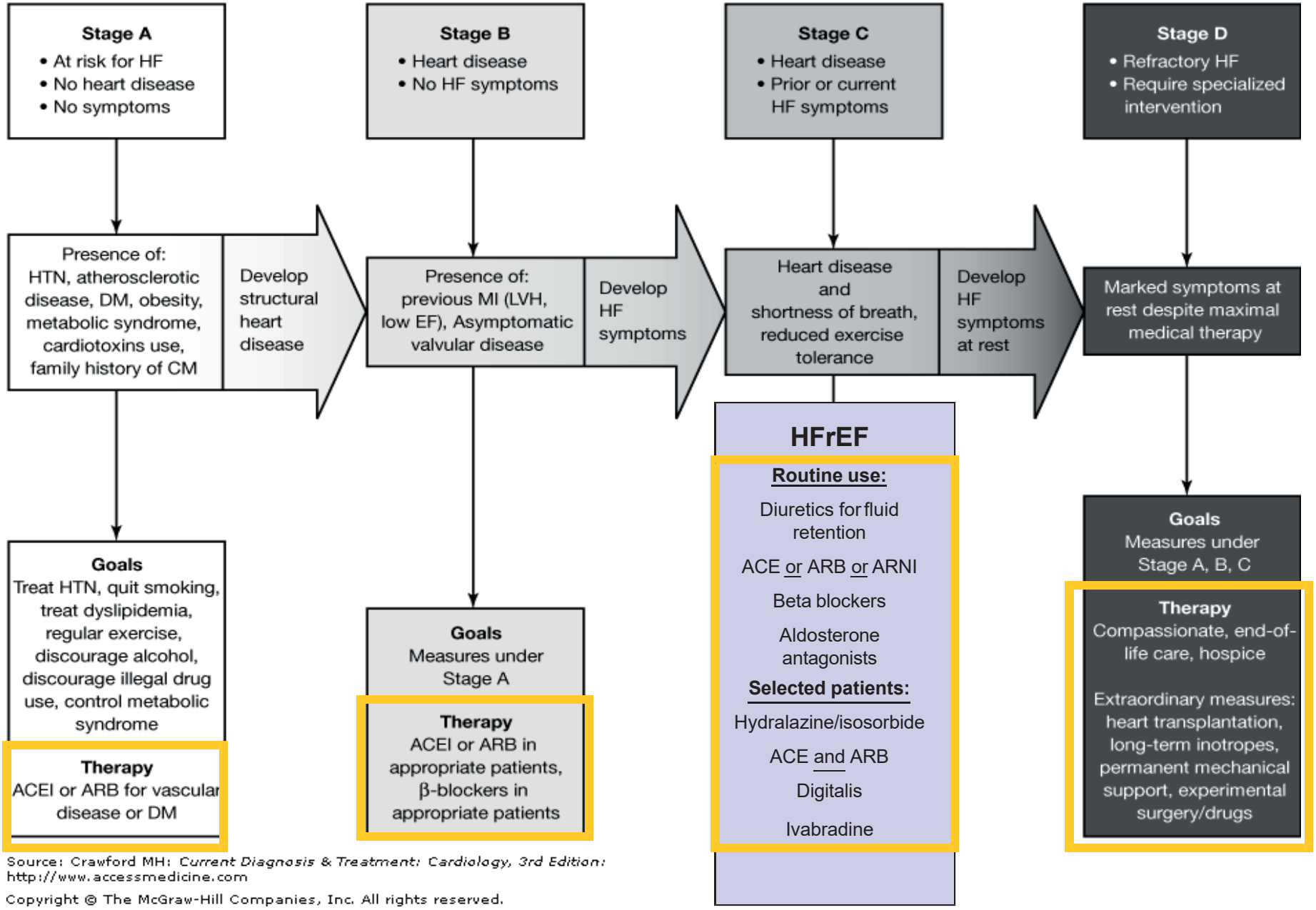
Medications to Decrease Mortality

- ACE inhibitors
- Beta Blockers (some)
- Aldosterone Antagonists
- Angiotensin Receptor Blockers (some)
- Hydralazine/Isosorbide Dinitrate combination
- Valsartan/Sacubitril combination

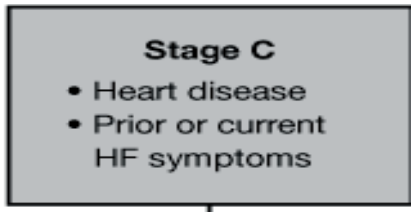
Identify medications that should be utilized in each stage (A to D) of the American College of Cardiology Foundation/American Heart Association staging system.

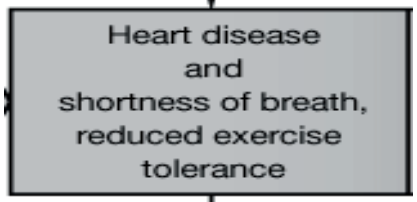
At Risk For Heart Failure

Heart Failure



Source: Crawford MH: *Current Diagnosis & Treatment: Cardiology, 3rd Edition*: http://www.accessmedicine.com





Stage C : with Symptoms or Prior Symptoms of HF and Structural Cardiac Dysfunction
Minimize HF Symptoms Prolong Survival

HFrEF

Routine use:
Diuretics: NYHA II-IV patients with fluid overload ACE or ARB: all patients NYHA I-IV

Beta blockers: all patients NYHA I-IV
Aldosterone antagonists: NYHA II-IV if CrCl > 30 mL/min and K < 5.0 mEq/L ARNI replaces ACE/ARB in patients with NYHA II-III

Selected patients:
Hydralazine/isosorbide: African Americans with NYHA III-IV with persistent symptoms ACE and ARB

Digitalis, Ivabradine

Stage A – Prevention of HF through 1 & 2CAD Prevention

- Smoking cessation
- Lipid management
- Blood pressure control
- Physical activity
- Weight management
- Diabetes management
- Appropriate medications
  - Beta-blockers, Renin-Angiotensin-Aldosterone system (RAAS) blockers, antiplatelets, statins, influenza vaccination

Treatment: Stage B

ACE inhibitors – All patients with LVEF ≤ 40%

Beta blockers – All patients with LVEF ≤ 40%

Pts with hx of MI/ACS and EF ≤ 40%:

- ACE inhibitors - prevent symptomatic HF and reduce mortality. ARBs ok if ACE not tolerated
- Beta blockers - reduce mortality
- Statins - prevent symptomatic HF and ASCVD events

Treatment: Stage B

Class IA – ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF. Captopril (SAVE), ramipril (AIRE), trandolapril (TRACE)

Class IA – In all patients with or without a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality. (Enalapril (SOLVD-prevention))

Class IA - In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated.– Valsartan (VALIANT)

Stage C:

Initial (Routine) Drug Therapy in stages A and B are also appropriate for patients in stage C

- loop diuretics ACE inhibitors ARBs, B-blocker

Additional drug entities have been proven to improve survival and reduce hospitalizations and improve symptoms

- Aldosterone antagonists
- Hydralazine/ISDN
- Angiotensin receptor and neprilysin inhibitor (ARNI)
- ACEi and ARB combination

Must consider symptom management

- Ivabradine
- Diuretics
- Digoxin

Stage C:

ACE inhibitors or ARBs	• All patients with HFrEF • May use ARB if intolerant of ACE
Selected beta blockers	• All patients with HFrEF • Bisoprolol, metoprolol succinate, carvedilol
Aldosterone receptor antagonists	• NYHA Class II-IV with LVEF ≤ 35% • Post-MI with LVEF ≤ 40% • Scr ≤ 2.5 mg/dL in men or ≤ 2.0 mg/dL in women, and K < 5.0 mEq/L
Diuretics	• Patients with volume overload to improve symptoms
Hydralazine + isosorbide dinitrate	• Black patients with NYHA class III–IV HFrEF on optimal therapy with ACE inhibitor and beta blocker • Symptomatic patients intolerant of ACE-I/ARB with HFrEF
Digoxin:	• Any patient with HFrEF, unless contraindicated, to decrease hospitalizations

Stage D Heart Failure

Persistent symptoms, refractory HF

- usually NYHA IV (rest)

On optimal standard therapy

- ACE/ARB, beta blocker, aldosterone antagonist, diuretic
  - may not tolerate agents (or may need smaller doses)
  - increased risk of hypotension and renal impairment (ACE, ARB) and worsening HF (beta blocker)
- may require sodium restriction to **2 grams/day or less**
- fluid restriction **(1.5 to 2 L per day)** is reasonable, especially in patients with hyponatremia

Stage D Heart Failure

Require specialized interventions

- Cardiac transplantation
- Mechanical circulatory support (VADs)
- **Positive inotropic agents**
  - **Continuous infusion** of inotrope reasonable for:
    - palliation of symptoms for end of life/hospice
    - if awaiting VAD or transplant
    - if hospitalized with decompensation, low blood pressure and impaired perfusion to organs
  - Routine **intermittent infusion** of inotrope is **not recommended**
    - once patient successfully weaned from inotrope
    - does not improve survival

Adapted From: 2013 ACCF/AHA Guideline for the Management of Heart Failure

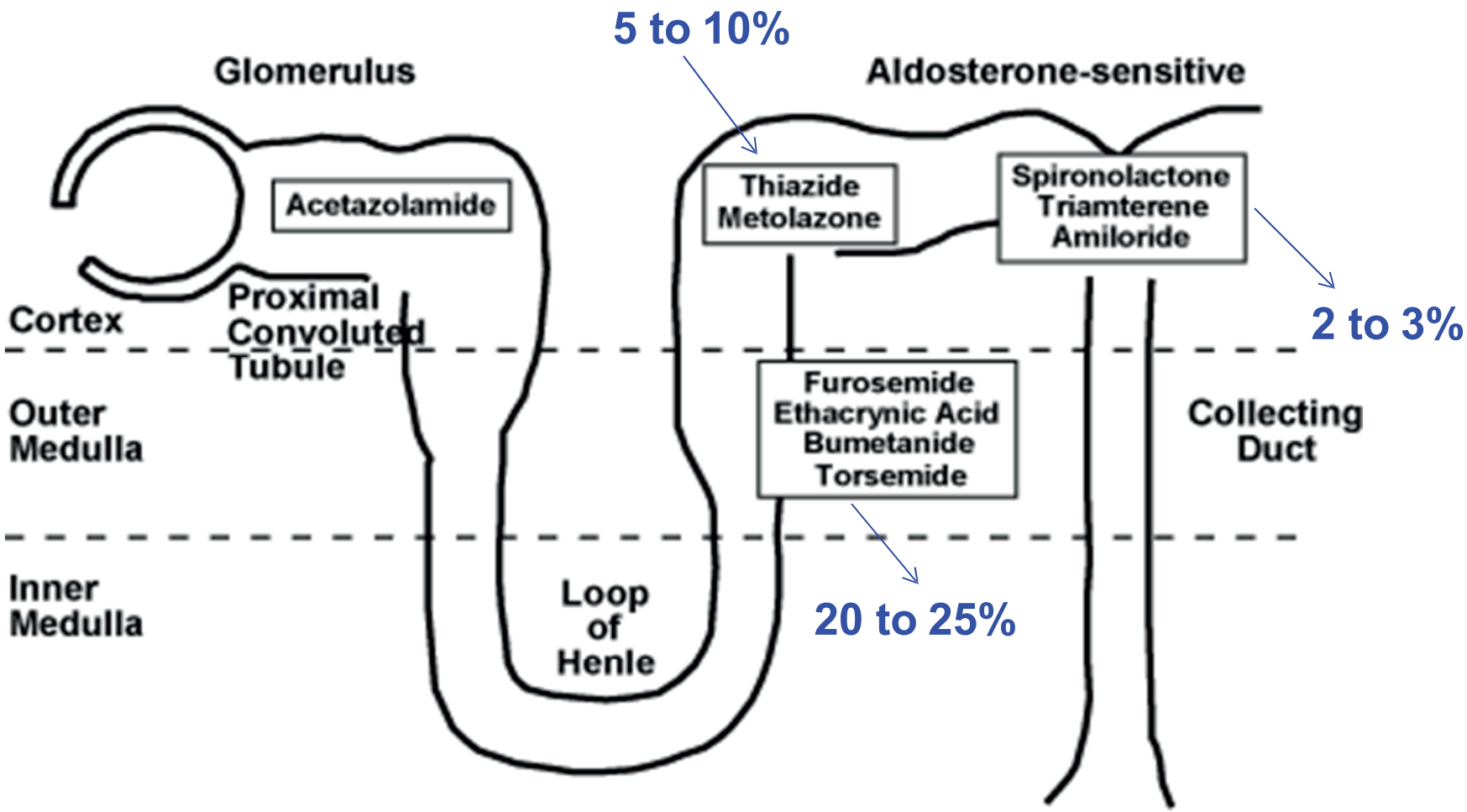
Describe the role of diuretics in the treatment of heart failure and make recommendations regarding appropriate use and monitoring.

Diuretic Use and Monitoring

- **Patients with HFrEF who have evidence of fluid retention, unless contraindicated**
  - achieve euvolemic state
  - continued in most patients with prior history of fluid retention to prevent recurrent fluid retention
  - loop diuretics preferred
  - initiate low dose and increase dose until urine output increases and weight decreases by ~ 0.5 to 1 kg/day
  - patients should monitor weight daily and contact provider for weight gain

Adapted From: 2013 ACCF/AHA Guideline for the Management of Heart Failure

Why Loop Diuretics?



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

Loop Diuretics

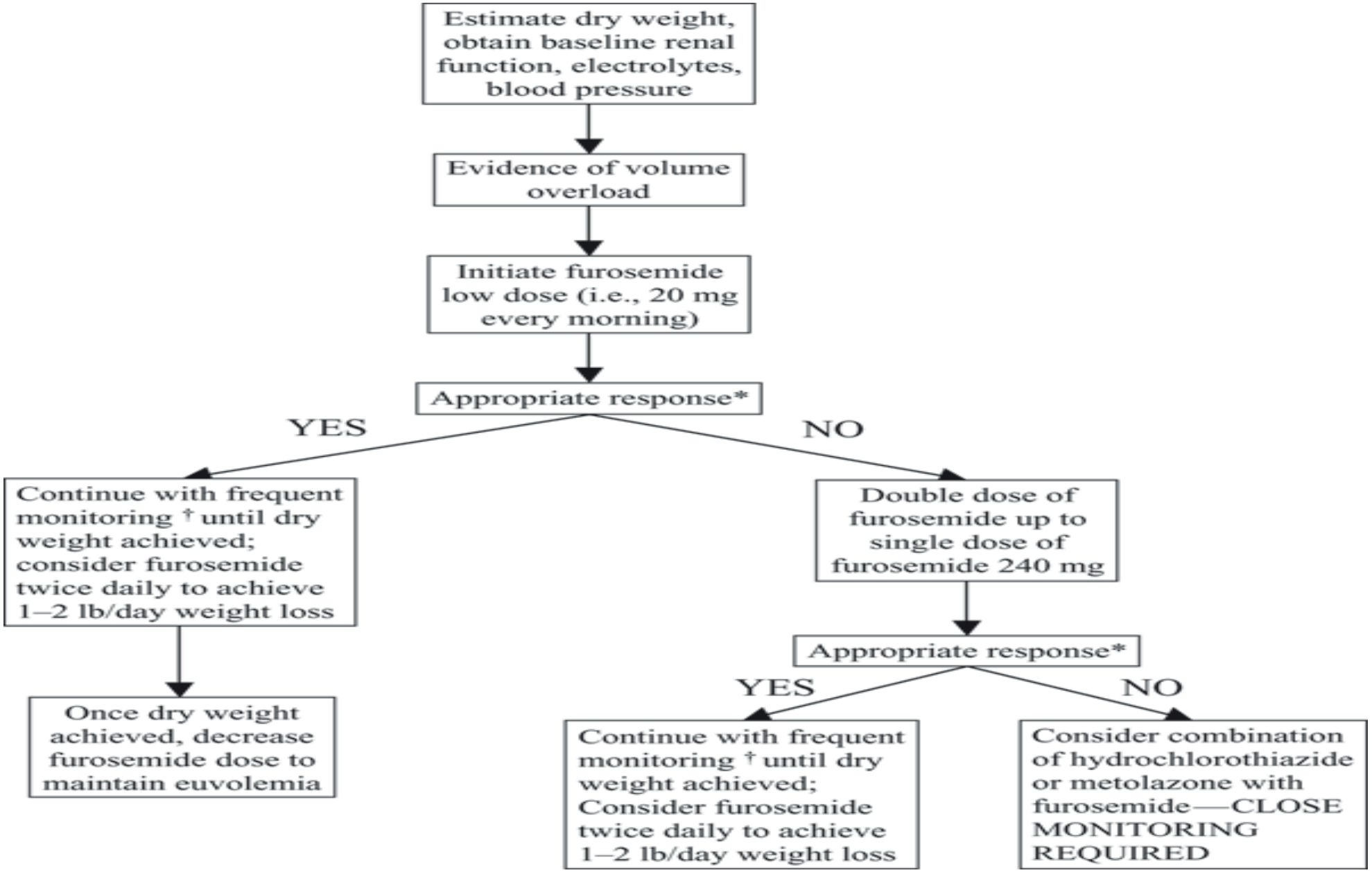
- Furosemide, bumetanide, torsemide, ethacrynic acid
  - Efficacy maintained in impaired renal function
  - Efficacy reduced by excess dietary sodium, NSAIDs
- Once ceiling dose reached, increase frequency for further diuresis
- Monitoring: **weight**, blood pressure, renal function, electrolytes (hypokalemia, hypomagnesemia), metabolic alkalosis

Loop Diuretics	Furosemide	Bumetanide	Torsemide
Initial daily dose (oral)	20 to 40 mg once or twice	0.5 to 1 mg once or twice	10 to 20 mg once
Maximum total daily dose (oral)	600 mg	10 mg	200 mg
Equivalent dose	**IV: 40 mg PO: variable (~ 80 mg)**	**IV: 1 mg PO: 1 mg**	**IV: 20 mg PO: 20 mg**
Pharmacokinetics (Oral)			
Bioavailability	**variable (average ~ 50%)**	**~ 80%**	**~ 80%**
Duration	6-8 hours	4-6 hours	~ 6-8 hours (may be longer)

Adapted From: Pharmacotherapy (Table 4-8, Drug Dosing), Lexi-Comp, and 2013 ACCF/AHA Guideline for the Management of Heart Failure

Loop Diuretics	Furosemide	Bumetanide	Torsemide
Ceiling dose (intravenous) **single dose above which additional response is unlikely to be observed**			
normal renal function	40 – 80 mg	1–2 mg	10-20 mg
moderate renal impairment	80-160 mg	4-8 mg	20-50 mg
severe renal impairment	160-200 mg	8–10 mg	50-100 mg

Brater DC. N Engl J Med 1998;339(6):387-95.

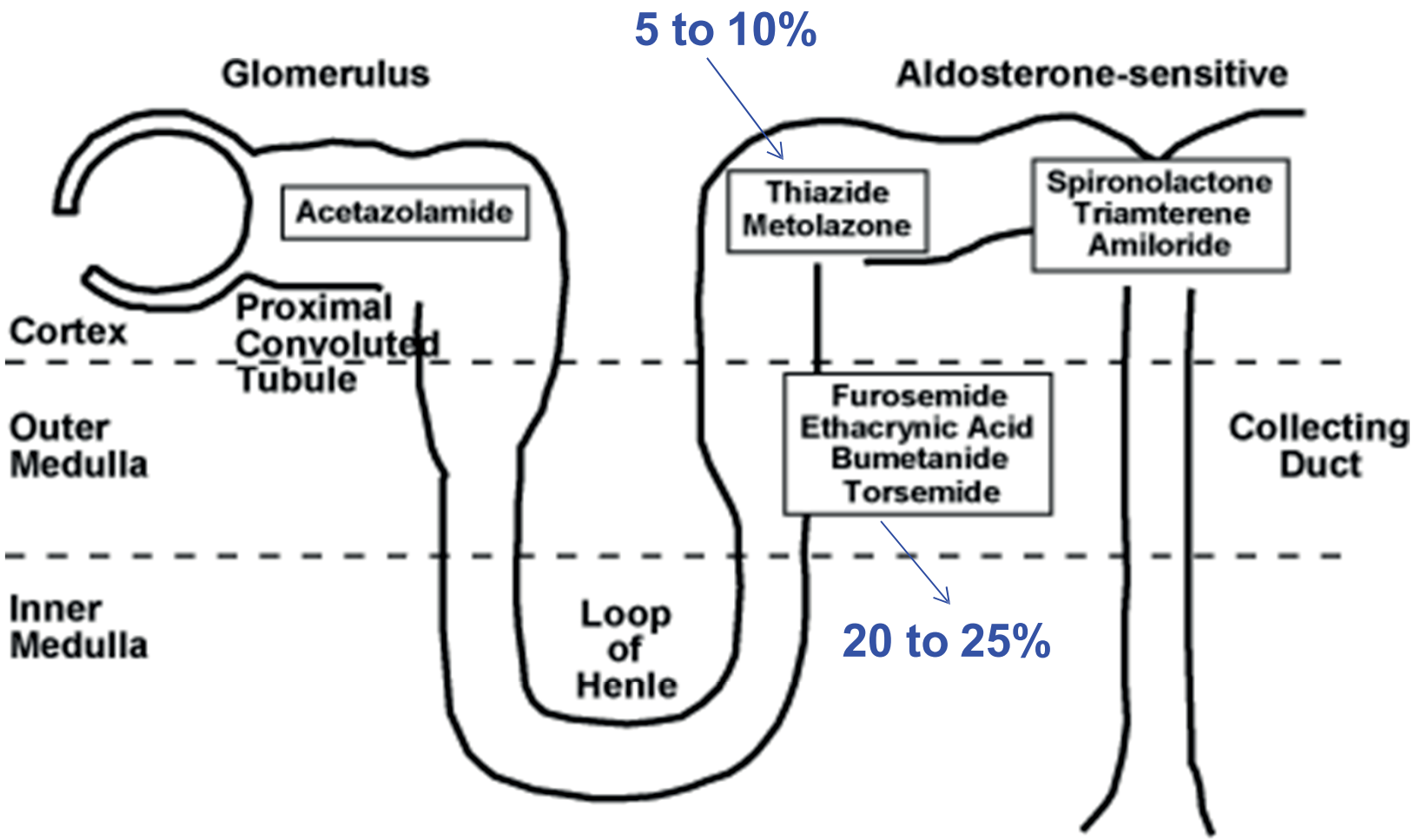


Source: Linn WD, Wofford MR, O'Keefe ME, Posey LM: *Pharmacotherapy in Primary Care:* http://www.accesspharmacy.com

Thiazide Diuretics

- Weaker than loop diuretics
  - Can be used for mild edema with HTN
- Decreased efficacy with renal impairment
  - metolazone (thiazide-like) can maintain efficacy
- Can use in addition to loop diuretics if needed to improve diuretic response
  - Example: metolazone 2.5 – 10 mg PO once daily- once weekly with loop diuretic
  - Give 30-60 min before loop diuretic in the morning

Why Combination Diuretics?



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

Diuretic Management

- **Volume Overload**
  - weight gain
  - jugular venous distension
  - hepatojugular reflux
  - pulmonary or systemic congestion
- **Volume Depletion**
  - weight loss
  - orthostasis/hypotension
  - tachycardia
  - dizziness
  - poor skin turgor
  - dry oral mucous membranes
  - Oliguria: decrease urine

Monitor: weight, vitals, intake/output, renal function, electrolytes (K and Mg)

Diuretic Management

Persistent volume overload limits efficacy and safety of other medications used for HF

Volume depletion increases risk of hypotension and worsening renal function

Initiating/titrating heart failure medications:

ACE inhibitors: may need to **decrease** diuretic dose

Beta blockers: may need to **increase** diuretic dose

Managing Diuretic Resistance

- Causes of diuretic resistance
  - Noncompliance
  - Drug interactions (NSAIDs)
  - Suboptimal dose
  - Absorption variability
  - Distal hypertrophy
- Managing diuretic resistance
  - Change dosing strategy
  - Switch diuretic
  - Sequential nephron blockade

Potassium Management

- Target range: 4 to 5 mEq/L
- General potassium replacement guidelines:
  - Potassium 3 to 3.9 mEq/L
    - Every 10 mEq increases potassium by ~0.1 mEq/L
    - Kcl 20meq q 2h for 2 doses or kcl 40meq once then recheck
    - Continue @ 20meq bid for 2-3 days
  - Potassium < 3 mEq/L
    - Every 10 mEq increases potassium by ~0.05 mEq/L
    - Give KCL 20 meg q 2h X 4 doses , then recheck
    - Continue at 20meq bid for 4-5 days

Discuss appropriate patient selection, initiation and dosage titration, and monitoring for the following heart failure therapies: angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and aldosterone antagonists.

ACE Inhibitors

HF Stage A,B,C,D

Improve survival 20-30%

Reduce combined risk of death or hospitalization

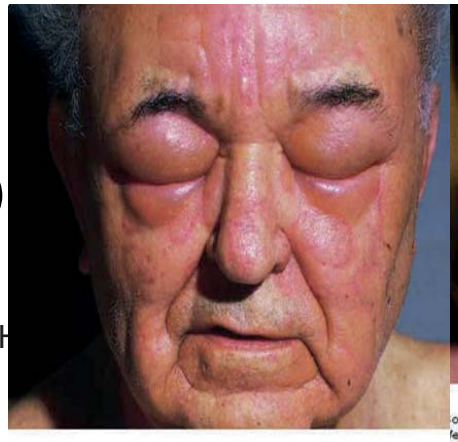
Slow the progression

Reduce rate of reinfarction

ACE Inhibitors

- **Contraindications**
  - angioedema
  - bilateral renal artery stenosis
  - pregnancy
- **Cautions**
  - renal insufficiency (SrCr > 3 mg/dL)
  - hyperkalemia (> 5.0 mEq/L)
  - hypotension (SBP < 80 mmHg)

Adapted From: 2013 ACCF/AHA Guideline for the Management of H



Source: Wolff K, Johnson RA, Suurmond, D: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Edition: http://www.accessmedicine.com.

ource: Knoop KJ, Stack LB, Storrow AB: *Atlas of Emergency* edicine, 2nd Edition: http://www.accessemergencymedicine.com

ACE Inhibitors

Initiation and Dosage Titration

Generic	Brand	Initial Dose	Target Dose (survival benefit)	Prodrug	Elimination
Captopril	Capoten	6.25 mg tid	50 mg tid	No	Renal
Enalapril	Vasotec	2.5 mg bid	10 – 20 mg bid	Yes	Renal
Lisinopril	Zestril, Prinivil	2.5–5 mg once daily	20–40 mg once daily	No	Renal
Ramipril	Altace	1.25–2.5 mg once daily	10 mg once daily (or 5 mg twice daily)	Yes	Renal
Trandolapril	Mavik	1 mg once daily	4 mg once daily	Yes	Renal/hepatic

Double dose ~ every 1-2 weeks, or as tolerated, until the highest tolerated dose or the target dose is reached.

Adapted From: Pharmacotherapy (Table 4-8, Drug Dosing), Lexi-Comp, and 2013 ACCF/AHA Guideline for the Management of Heart Failure

ACE Inhibitors

Blood pressure

Renal function

- Maintain optimal fluid status (avoid over-diuresis)
- SrCr may increase due to renal efferent arteriolar dilation (slightly ↓ GFR)
  - 30% increase (within first 2 months) is usually acceptable

Hyperkalemia

- Especially in decreased renal function or taking other medications which increase potassium

*Monitor renal function and potassium 1-2 weeks after initiation and dosage titration

Cough (up to 20%)

- Dry, tickle – usually appears within months
- Disappears 1-2 weeks after stopping ACE inhibitor
- Can switch to ARB

Angioedema (less than 1%)

- Avoid all ACE inhibitors
- Can cautiously try ARB

Angiotensin Receptor Blockers ARB

ARBs block angiotensin II produced by non-ACE enzymatic pathways (more complete blockade of angiotensin II)

no effect on bradykinin (lower incidence of cough)

valsartan and candesartan have shown benefit in trials for HF; losartan with higher doses

Relationship between ARB dose and clinical outcome not extensively studied

Dosage Titration

- High-Dose versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure Trial
- randomized patients intolerant of ACE inhibitor to losartan 50 mg daily or losartan 150 mg daily
- patients receiving higher losartan dose had significant reduction in combined endpoint of death or heart failure hospitalization

Angiotensin Receptor Blockers

Initiation and Dosage Titration

Drug	Initial Dose	Target Dose
candesartan	4 – 8 mg once daily	32 mg once daily
losartan	25 – 50 mg once daily	150 mg once daily
valsartan	20 – 40 mg twice daily	160 mg twice daily

Adapted From: Pharmacotherapy (Table 4-8, Drug Dosing), Lexi-Comp, and 2013 ACCF/AHA Guideline for the Management of Heart Failure

Angiotensin Receptor Blockers

Appropriate Use

- Reasonable to use as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications
- Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended

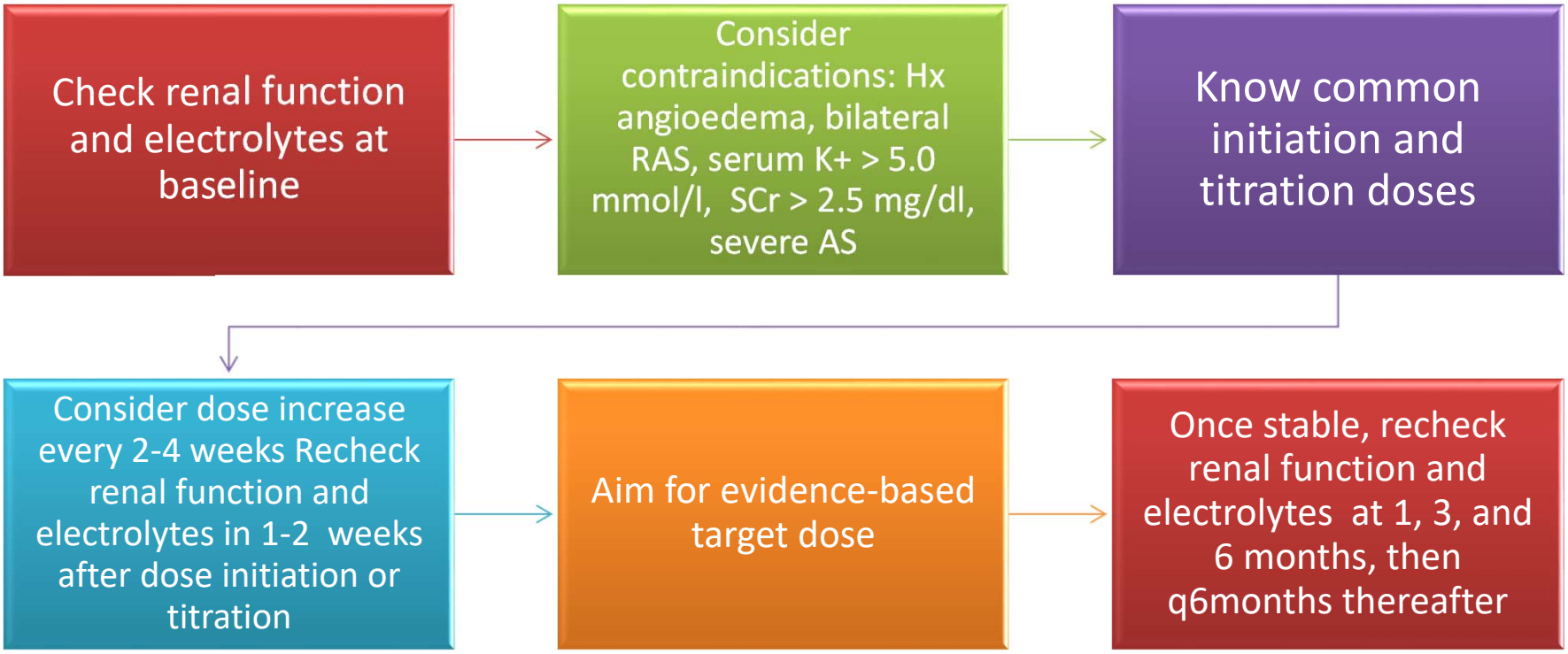
Angiotensin II receptor blockers in patients with current or prior symptoms of HF and reduced EF who are **ACE inhibitor-intolerant**

- **history of angioedema (use caution with ARB)**

CHARM-Alternative Trial: tolerability of ARB in patient who cannot take an ACE inhibitor

- ACE inhibitor: 704 patients with cough
  - candesartan discontinued in 2 patients (~0.3%)
- ACE inhibitor: 39 patients with prior angioedema
  - candesartan discontinued in 1 patient (~2.6%)

How to Use an ACEi or ARB

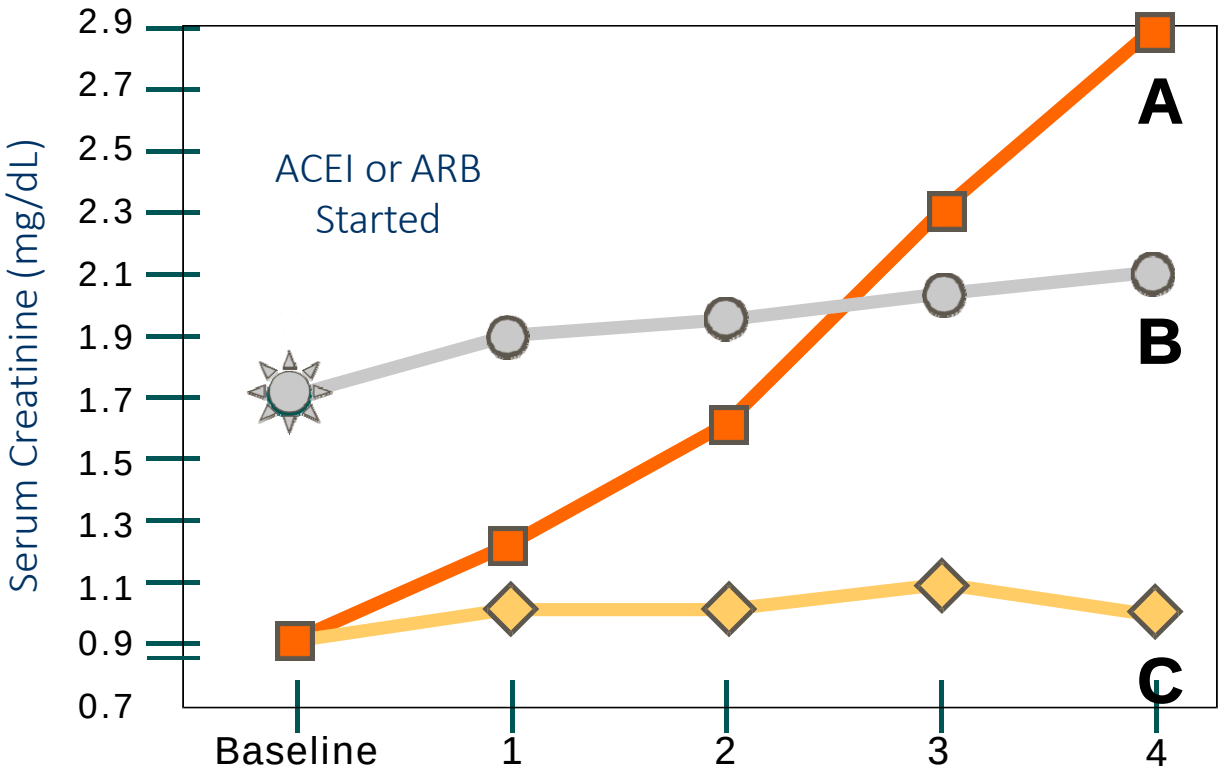


How to Use an ACEi or ARB

Common problems

- Cough – switch to ARB
- **Hyperkalemia**
  - Check for other offenders
  - If less than 6.0 mmol/l and greater than 5.5 mmol/l – half- dose
  - If greater than 6.0 mmol/l - discontinue
- **SYMPTOMATIC hypotension**
  - Reduce diuretic or other antihypertensives
  - May reduce dose or discontinue if absolutely needed
- **Worsening renal function**
  - Next slide

ACEi and Worsening Renal function



If SCr Increases

- Check for other nephrotoxic meds
- ↑ SCr up to 30% from baseline may be acceptable
- May half or discontinue based on relative increase or absolute value

Bakris GL. Arch Intern Med 2000;160:685-693

Sacubitril/Valsartan

ARB + neprilysin inhibitor

- Increases natriuretic peptides and causes vasodilation

Indication

- Reduce risk of heart failure in patients with HFrEF and NYHA II-IV
- Used in place of ACE or ARB
- NEVER in combination with ACE

Sacubitril/Valsartan Dosing

Initial: valsartan 51mg and sacubitril 49mg BID

- Titration: double the dose as tolerated after 2-4 weeks

Target maintenance dose: valsartan 103mg sacubitril 97mg and BID

Allow a 36 hour washout period when switching from or to an ACE inhibitor

- If previously taking low dose ACE or ARB
  - Initial: valsartan 26mg and sacubitril 24mg BID

Renal and hepatic dosing

- eGFR ≤ 30 or moderate hepatic impairment
- Initial: valsartan 26mg and sacubitril 24mg BID

Sacubitril/Valsartan

Contraindications

- **History of angioedema**
- Concomitant ACE-I use or use within 36 hour
- Concomitant use of aliskiren DM patients
- Pregnancy

Side Effects

- Hypotension, Hyperkalemia, Increased SCr, Angioedema, Cough – 9%

Place in Therapy

- In 2016 guideline update
- NYHA II-III who tolerate ACE or ARB, replacement with ARNI is recommended for further reduction in morbidity and mortality Reduces symptoms, exacerbations, mortality

Availability

- combination tablets sacubitril/valsartan, brand Entresto 24/26 mg, 49/51 mg, 97/103 mg

Beta Blockers

Patient Selection

- HF Stage B, C, D
  - Majority of data in NYHA II and III patients
  - Studies in NYHA I and IV patients
- Initiate in stable heart failure:
  - not hospitalized in intensive care unit
  - did not require recent treatment with intravenous positive inotrope

Contraindications

- Asthma, severe bradycardia (HR < 50 bpm), AV block (second or third degree) without pacemaker

Cautions

- reactive airway disease, diabetic, cocaine use, vasospastic angina

Monitoring

- fluid retention, worsening heart failure, fatigue, weakness BP, HR, dizziness

Beta Blockers

Initiation and Dosage Titration

Drug	Starting Dose	Target Dose <85 kg	Target Dose > 85 kg
Bisoprolol	1.25 mg daily	5 mg daily	10 mg daily
Carvedilol	3.125 mg bid	25 mg bid	50 mg BID
Metoprolol succinate XL	12.5 mg daily * 25 mg daily **	200 mg daily	200 mg daily
Nebivolol***	1.25 mg daily	10 mg daily	10 mg daily

Double dose ~ every 2 weeks, or as tolerated, until the highest tolerated dose or the target dose is reached.

* NYHA Class II

**NYHA Class III and IV

***Not FDA approved for heart failure

Carvedilol
Immediate and Extended Release

Daily Dose of Immediate Release Carvedilol Tablets	**Daily Dose of Extended Release Carvedilol CR Capsules (lower bioavailability)**
6.25 mg (3.125 mg twice daily)	10 mg once daily
12.5 mg (6.25 mg twice daily)	20 mg once daily
25 mg (12.5 mg twice daily)	40 mg once daily
50 mg (25 mg twice daily)	80 mg once daily

Carvedilol vs Metoprolol Succinate

No data directly comparing

Carvedilol

- Beta non-selective + alpha blocking activity
- BID dosing

Metoprolol succinate

- Beta-1 selective
- Daily dosing

Aldosterone Antagonist

Patient Selection : Appropriate patient

- **HF Stage C and D**
- **NYHA II-IV patients with an EF ≤ 35%, unless contraindicated**
  - Previously reserved for NYHA III-IV patients with moderately severe to severe symptoms; spironolactone (RALES Trial)
  - NYHA II patients :should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels; eplerenone (EMPHASIS-HF Trial)
  - After MI in patients with EF ≤ 40% with symptoms of HF or history of diabetes; eplerenone (EPHESUS Trial)

Aldosterone Antagonist

Determine if contraindications exist:

- SrCr should be < 2.5 mg/dL in men or < 2.0 mg/dL in women
- OR estimated CrCl/GFR > 30 mL/min/1.73 m2
- baseline potassium should be < 5.0 mEq/L

Eplerenone is a more selective aldosterone antagonist

Aldosterone Antagonist

Spironolactone

- **Initial dose is 12.5 – 25 mg once daily**
  - CrCl/GFR 30-49 mL/min/1.73 m^2: 12.5 mg **once daily or every other day**
  - CrCl/GFR < 30 mL/min/1.73 m^2: do not start
- **Maximum dose:25 – 50 mg once daily**
  - CrCl/GFR 30-49 mL/min/1.73 m^2: 12.5 – 25 mg once daily

Eplerenone

- **Initial dose is 25 mg once daily or every other day**
  - CrCl/GFR 30-49 mL/min/1.73 m^2: 25 mg once every other day
  - CrCl/GFR < 30 mL/min/1.73 m^2: do not start
- **Maximum dose: 25-50 mg once daily**
  - CrCl/GFR 30-49 mL/min/1.73 m^2: 25 mg once daily

Aldosterone Antagonist Monitoring

Recheck renal function and electrolytes in 1 week and 1 month after starting and dose titration

Consider dose increase in 4-8 weeks

Recheck renal function and electrolytes in monthly for first 3 months, every 3 months for the rest of year, then q4months

gynecomastia

- ~10% spironolactone
  - related to dose and duration
- < 1% eplerenone

Common Problems with AAs

Breast tenderness and/or enlargement

- Switch to eplerenone

Worsening renal function

- May half or discontinue based on increase in SCr or decrease in CrCl

Hyperkalemia

- If > 5.5 mmol/l, half dose or take every other day
- If > 6.0 mmol/l, discontinue

Reducing Hyperkalemia Risk

Start with low doses: especially in following patients: elderly, low muscle mass , renal impairment

Decrease/discontinue potassium supplements when starting an aldosterone antagonist

Avoid ACE inhibitor, ARB, and aldosterone antagonist triple therapy

may need to avoid high doses of ACE or ARB

Reducing Hyperkalemia Risk

Monitor serum potassium and renal function

- within 3 days and 1 week after initiation or dose titration
  - then monthly for the first 3 months
  - then every 3 months

Patient counseling:

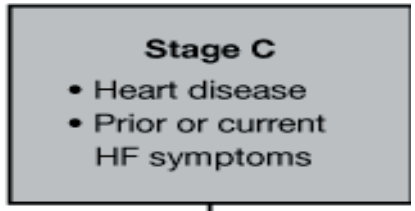
- limit intake of high potassium containing foods and salt substitutes
- avoid concomitant NSAIDs or COX-2 inhibitors
- may need to temporarily stop aldosterone antagonist if diuretic therapy is held or dehydration occurs

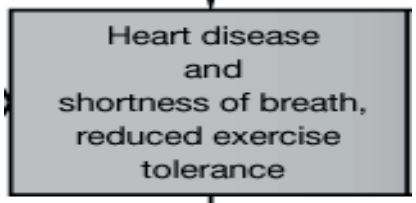
HFrEF Stage C

ADDITIONAL DRUG THERAPY (FOR SELECTED PATIENTS)

HYDRALAZINE/ISOSORBIDE DINITRATE DIGOXIN

IVABRADINE





HFrEF

Routine use:

Diuretics: NYHA II-IV patients with fluid overload

ACE or ARB: all patients NYHA I-IV

Beta blockers: all patients NYHA I-IV

Aldosterone antagonists: NYHA II-IV if CrCl > 30 mL/min and K < 5.0 mEq/L

ARNI replaces ACE/ARB in patients with NYHA II-III

Selected patients:

Hydralazine/isosorbide: African Americans with NYHA III-IV with persistent symptoms

ACE and ARB

Digitalis, Ivabradine

Differentiate between the role of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and the combination of hydralazine and nitrate therapy in the treatment of heart failure.

Hydralazine/Isosorbide Dinitrate

Combination

- Hydralazine: direct arterial vasodilator leads to decreased SVR (decreased afterload)
- antioxydants properties, prevents nitrate tolerance
- Nitrates: nitric oxide donors lead to venous vasodilation (decreased preload)
- Disadvantages of combination regimen: frequent dosing (several times a day) and side effects

Hydralazine side effects:

- Hypotension
- Reflex tachycardia
- GI distress
- Drug-induced lupus-like syndrome with larger doses, longer duration: fever, arthralgia, malaise, , maculopapular facial rash
- Blood dyscrasias: agranulocytosis, anemia, leukopenia, thrombocytopenia
- Others: headache, dizziness, flushing, palpitations

Hydralazine/Isosorbide Dinitrate

Isosorbide dinitrate side effects:

- Hypotension
- Tachycardia
- Dizziness, syncope
- Headache, flushing
- Nitrate tolerance is prevented by use of hydralazine

Appropriate Use

- **In place of an ACE inhibitor or ARB for patients with HFrEF who develop renal impairment, hyperkalemia, or angioedema**
- V-HeFT I Trial (vs. placebo):greater reduction in mortality with hydralazine/isosorbide
- V-HeFT II Trial (vs. enalapril):greater reduction in mortality with enalapril
- Post-hoc retrospective analysis of trials: greater efficacy with hydralazine/isosorbide in African-American patients

Hydralazine/Isosorbide Dinitrate appropriate use

In place of an ACE inhibitor or ARB for patients with HFrEF who develop renal impairment, hyperkalemia, or angioedema

V-HeFT I Trial (vs. placebo):greater reduction in mortality with hydralazine/isosorbide	V-HeFT II Trial (vs. enalapril):greater reduction in mortality with enalapril	Post-hoc retrospective analysis of trials: greater efficacy with hydralazine/isosorbide in African-American patients

Hydralazine/Isosorbide Dinitrate appropriate use

Self-described **African-American patients** with NYHA III-IV HFrEF **on optimal therapy** with ACE inhibitors and beta blockers

African-American Heart Failure Trial (A-HeFT)	BiDil ® :1 tablet (20mg isosorbide dinitrate, 37.5 mg hydralazine) 3 times/day; titrate to a maximum dose of 2 tablets 3 times/day	If given separately • Hydralazine 25-50mg 3 or 4 times daily (max 300mg/day) plus isosorbide dinitrate 20-30 mg 3 or 4 times daily (max 120mg/day)

Describe the role of digoxin in the treatment of heart failure, and make recommendations regarding appropriate use and monitoring.

Digoxin

MOI:

- inhibit sodium potassium ATPase
- cardiac tissue: increase contractile state, positive inotrope (minimal)
- non-cardiac tissue: attenuate neurohormonal activation
- reduces sympathetic outflow from CNS and excessive SNS activation; reduces renal tubular reabsorption of sodium; and suppresses renin release from kidney

Dosing

- Dosing: 0.125 to 0.25 mg daily,Also available in low dose 62.5 mcg (Lanoxin)
  - Use 0.125 mg daily or every other day if:
    - > 70 years old, impaired renal function, and/or low lean body mass
  - Do not use a loading dose for HF
  - Bioavailablity varies with products

Digoxin

Appropriate Use

- Can be beneficial in patients with HFrEF to decrease hospitalizations
- persistent symptoms despite use of neurohormonal antagonists
- lack of response to other therapies
- cannot tolerate other therapies

Monitoring

- heart rate, EKG,electrolytes (potassium, magnesium, calcium)
- serum creatinine
- drug interactions
- side effects, signs and symptoms of toxicity

Digoxin Therapeutic Serum Drug Levels

draw trough level (before next dose) at steady state (~7-10 days if normal renal function)

avoid the long distribution phase: draw level at least 6-8 hours after last dose

therapeutic serum drug level: 0.5 to 0.9 ng/mL

toxicity: > 2 ng/mL

- risk increased with age, renal impairment
- can also occur with lower levels - especially with hypokalemia, hypomagnesemia, hypercalcemia, or drug interactions
- K competes with digoxin binding on Na+/K+-ATPase (low K increases digoxin binding and enhances therapeutic/toxic effects)
- Low Mg reduces intracellular potassium
- High Ca enhances digoxin increases in intracellular Ca (calcium overload) and increases susceptibility to arrhythmias

Digoxin

Drug interactions

- Major drug interactions that decrease digoxin clearance (require digoxin dose reduction):
- amiodarone, dronedarone, propafenone, quinidine
- verapamil, diltiazem, cyclosporine, clarithromycin, erythromycin, itraconazole

Noncardiac adverse effects:

- Mostly neurological and gastrointestinal
- anorexia, nausea, vomiting, abdominal pain
- visual disturbances: halos, photophobia, problems with color perception
- fatigue, weakness, headache, neuralgia, confusion, delirium, psychosis

Digoxin

Cardiac adverse effects

- ventricular or atrial arrhythmias
- ventricular tachycardia, ventricular fibrillation
- atrioventricular (AV) block
- AV junctional escape rhythms
- junctional tachycardia
- sinus bradycardia

Withdrawal

- PROVED and RADIANCE Trials
- digoxin withdrawal: worsening heart failure, decreased exercise capacity, and reduction in EF
- Post hoc analysis of DIG Trial
- digoxin withdrawal: increased risk of all cause hospitalization and heart failure-related hospitalization
- Continue digoxin unless toxicity or serious adverse events occur

Calcium Channel Blockers

Appropriate Use

- Calcium channel-blocking drugs are not recommended as routine treatment for HFrEF

Avoid verapamil and diltiazem if reduced EF

Amlodipine – neutral effect on mortality in patients with reduced EF

- Use only if further BP or ischemia control is needed despite standard HF medications (at target or highest tolerated doses)

Calcium Channel Blockers Pharmacodynamic Differences -

Dihydropyridines – vascular type calcium channels

- Nifedipine, amlodipine, felodipine
- More potent vasodilators than non-dihydropyridines

Non-dihydropyridines – cardiac type calcium channels

- Verapamil, diltiazem
- Verapamil more selective for cardiac than diltiazem
- Depress sinus node and slow AV conduction
- Decrease myocardial contractility

Ivabradine

Inhibits the I_f (funny) current in the heart

Indication: reduction of hospitalization in HF patients with

- Stable, symptomatic HF, Documented hospital admission for worsening heart
- LVEF ≤ 35%
- Sinus rhythm with resting HR ≥ 70 bpm
- On max tolerated beta blocker dose or have a contraindication

Ivabradine

Dosing

- Initial: 5mg BID or 2.5mg BID if history of conduction defects or bradycardia
- Titrate: increase dose to achieve resting HR 50-60 bpm
- Max: 7.5mg BID

Contraindications

- ADHF
- BP < 90/50
- Conduction abnormalities
- Resting HR < 60 bmp
- Pacemaker dependent
- Strong CYP3A4 inhibitors

Ivabradine

Side Effects

- Atrial fibrillation, Bradycardia, Heart block, Hypertension
- Vision – phosphenes

Place in therapy

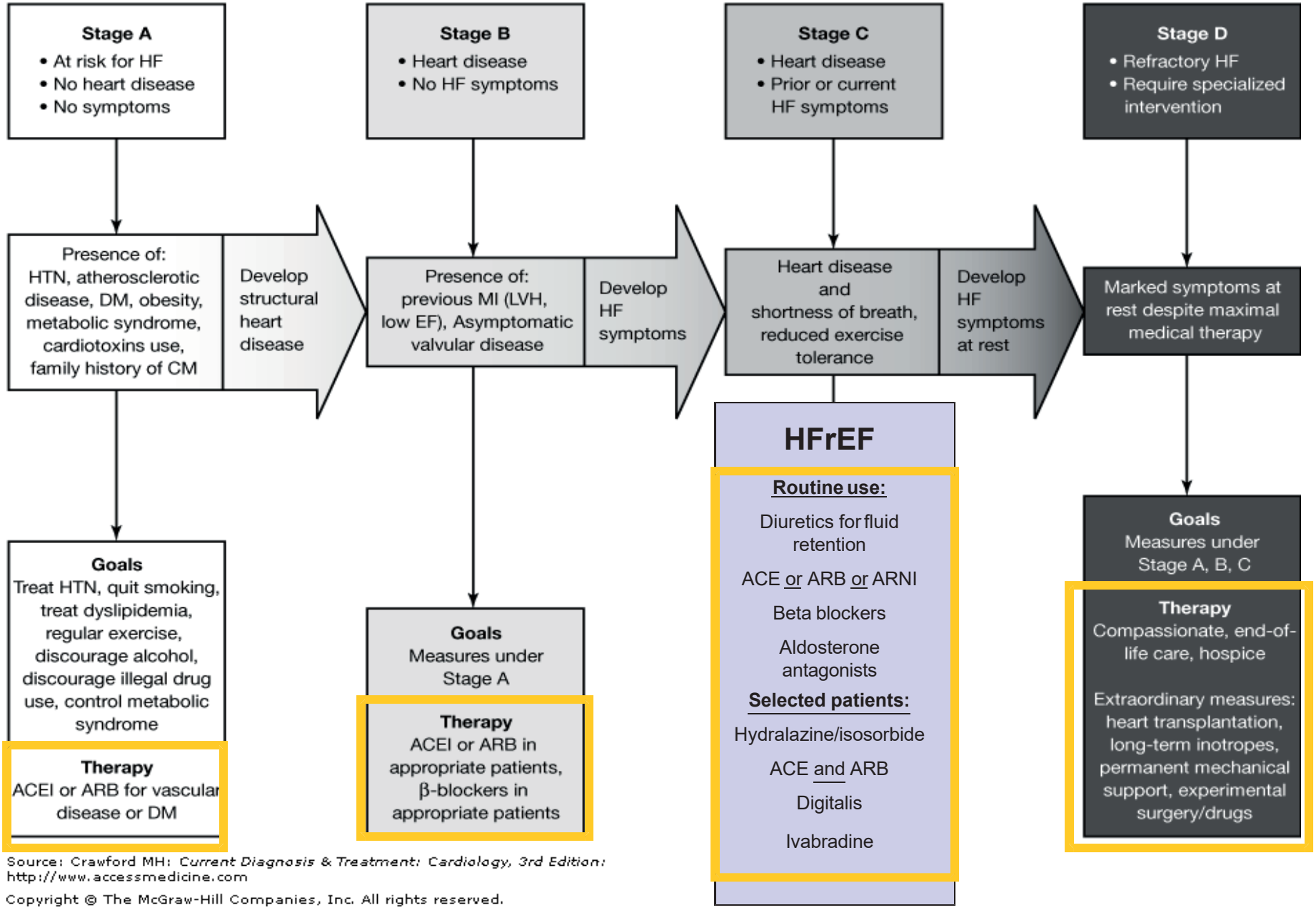
- In 2016 guideline update
- Add on to patients with NYHA II-III stable chronic HF with LVEF ≤ 35% who are already receiving treatment including beta blocker at max dose
- Sinus rhythm with resting HR ≥ 70 bpm
- Reduces hospitalizations, not mortality

Available strengths : 5mg and 7.5mg

Design and redesign an appropriate pharmacotherapy regimen and monitoring plan to positively impact morbidity and mortality for patients in heart failure stages A to D.

At Risk For Heart Failure

Heart Failure



Source: Crawford MH: *Current Diagnosis & Treatment: Cardiology, 3rd Edition*: http://www.accessmedicine.com

Chronic Heart Failure Preserved Ejection Fraction (HFpEF)

HFpEF

Preserved ejection fraction

- EF > 50%

Abnormal diastolic function

- impaired (incomplete) ventricular relaxation and filling during diastole
- increased diastolic ventricular stiffness

Treatment Goals:

- relief of symptoms
  - **diuretics** for relief of symptoms from volume overload
- optimize myocardial filling in diastole
  - relief of underlying factors that contribute to diastolic dysfunction:
- hypertension
  - **use of beta blockers, ACE inhibitors, and ARBs** is reasonable
- **tachycardia**, atrial fibrillation, ischemia

HFpEF

Major Treatment Differences

- **Use of negative chronotropes**
  - prolong diastolic filling time
  - target resting HR 60 bpm
  - beta blockers (any agent, slow initiation/titration is not as important as with reduced EF)
  - verapamil, diltiazem can be used
- **Use of digoxin**
  - use to minimize symptoms is not well established
  - can be used as a negative chronotrope if needed to control HR in atrial fibrillation

HFpEF

Mortality benefit of neurohormonal blockade?

- **Evidence is <u>less clear</u> than HFrEF; inconsistent trial results**

ACE/ARB – no effect on mortality (candesartan, irbesartan, perindopril)

- **consider use of ARB to decrease HF hospitalizations**
- (candesartan, CHARM-Preserved Trial

beta blocker decreased mortality (propranolol, nebivolol); no effect on mortality (carvedilol)

spironolactone – no effect on mortality; decreased HF hospitalizations

Monitoring of HF

Serial renal function and serum electrolytes

Daily weights (self-monitor)

- Call doctor if 1 lb in 24 hours, 3 lbs in 1 week

Fluid and sodium intake

Ability to sleep lying down/orthopnea

- Where does patient sleep?
- How many pillows do they need?

Medication adherence

Summary

Evaluating patients in the community:

- Shortness of breath
  - At rest
  - On exertion
  - Laying down

Medication adherence

Weight (daily)

Edema

Treatment is dependent on staging and symptoms

Most patients with HFrEF should be on:

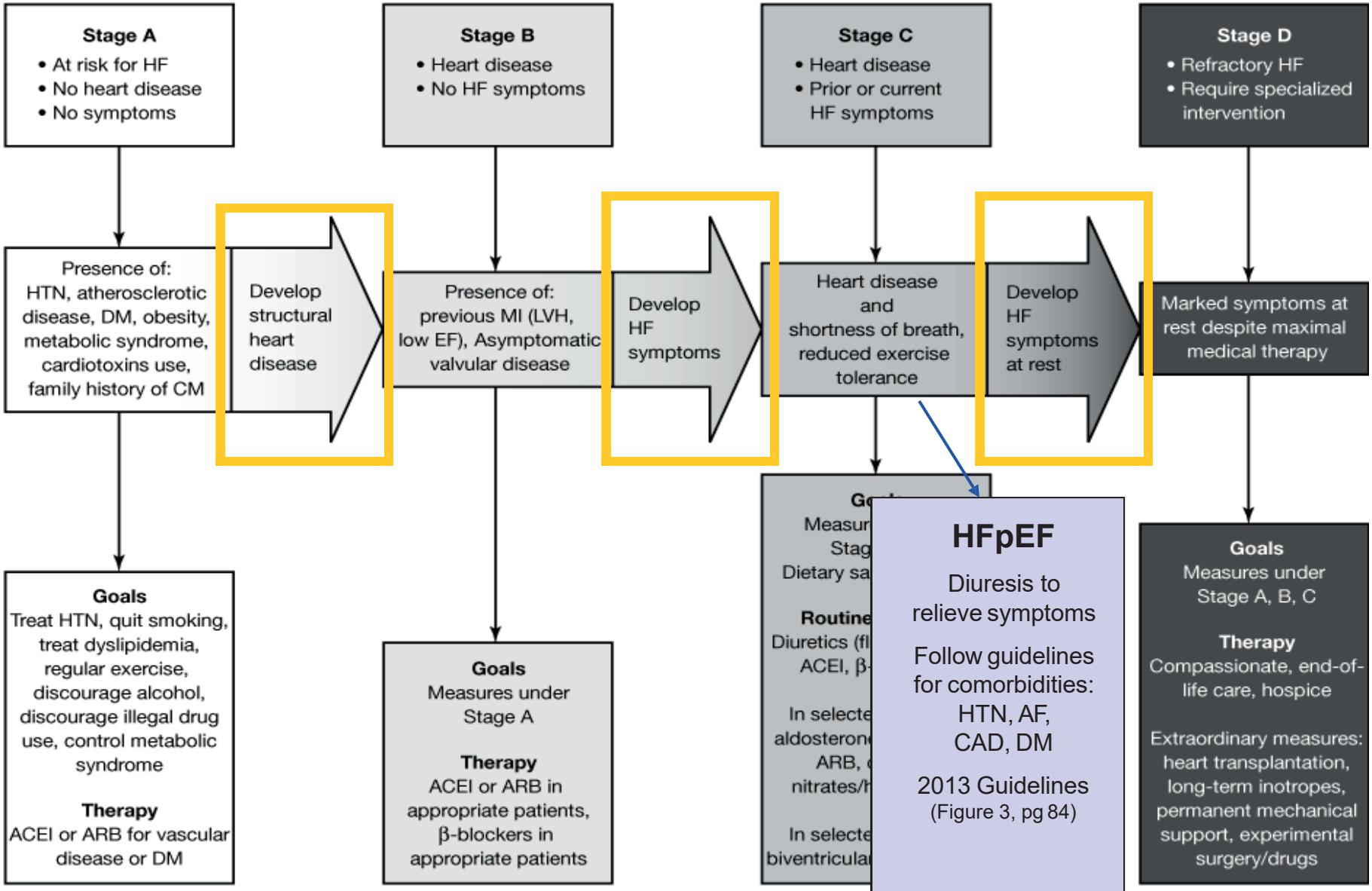
- ACE inhibitor
- Beta blocker
- Diuretic (if fluid overloaded)

Selected patients with HF may be on:

- Aldosterone antagonist
- Nitrate + Hydralazine
- CCB
- Digoxin

At Risk For Heart Failure

Heart Failure



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Stages in the Development of HF