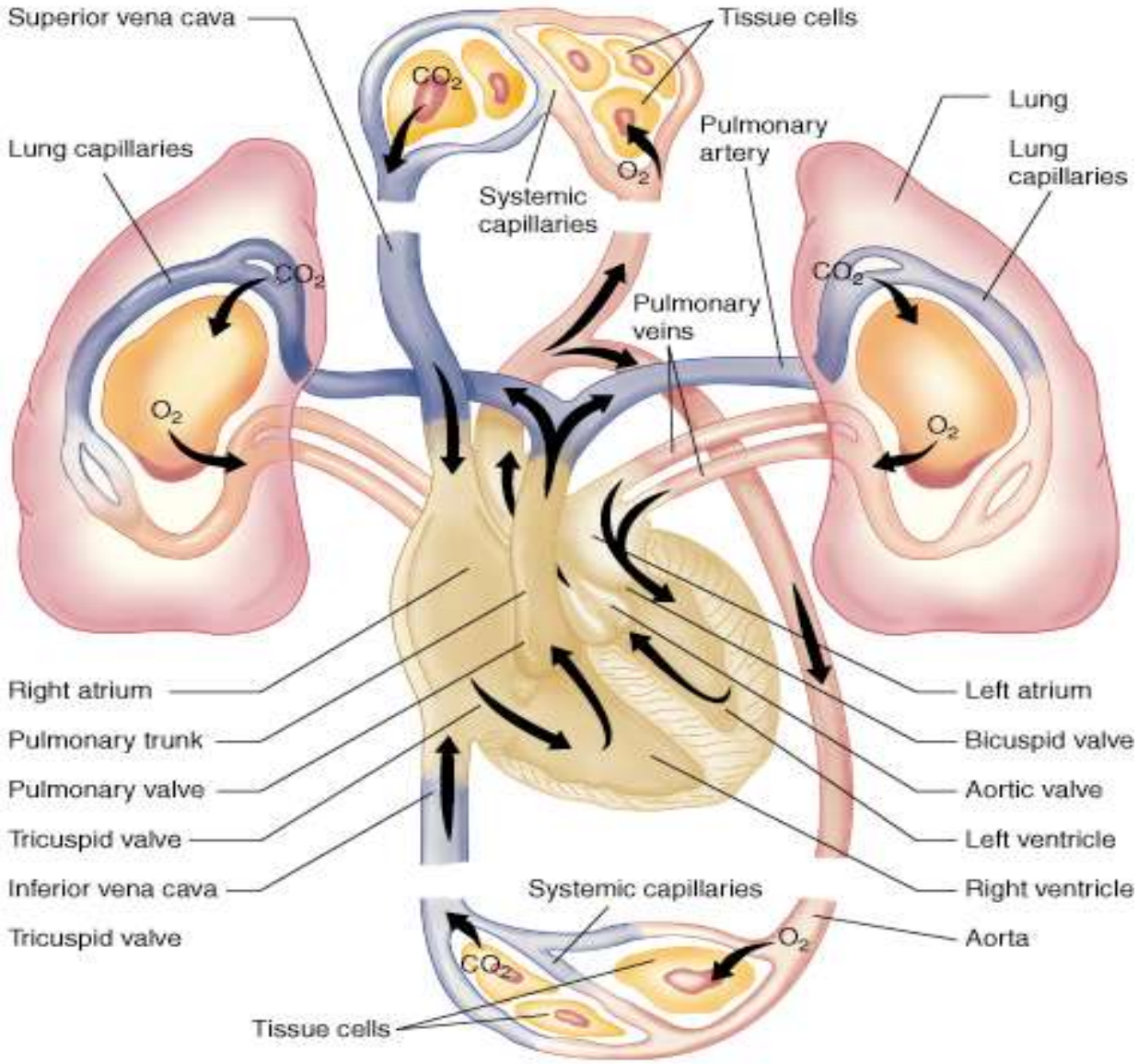
Cardiovascular System Testing



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the cardinal symptoms of coronary artery disease & CHF.
2. Describe the various serum biomarkers & their utility in providing diagnostic & prognostic information related to myocardial injury.
3. Differentiate between exercise & pharmacologic stress testing & the methods used to detect myocardial ischemia
4. Outline the role of cardiac catheterization & angiography in the Dx & management of subjects with coronary artery disease.
5. List three echocardiographic methods & describe their role in assessing cardiac structure & function.
6. Describe the use of dobutamine, dipyridamole, & adenosine in so-called pharmacologic stress testing.

CV Testing: Introduction

- CV disease is the every State's leading killer for both men & women among all racial & ethnic groups.
- A thorough CV assessment will help to identify significant factors that can influence CV health such as high blood cholesterol, cigarette use, diabetes, or HTN.
- Atherosclerosis, the cause of most CVD events, is typically present for decades before symptoms appear.
- With a thorough Hx, comprehensive physical examination, & appropriate testing, the individual with subclinical CVD usually can be identified, & the subject with symptomatic CVD can be assessed for the risk of an adverse event & can be managed appropriately.

The Hx

- The elements of a comprehensive Hx include the chief complaint, current symptoms, past medical Hx, family Hx, social Hx, & review of systems.
- **Chief complaint-** The patient is asked to describe his or her current symptoms, including their duration, quality, frequency, severity, progression, precipitating & relieving factors, associated symptoms, & impact on daily activities.
- The past medical Hx may reveal previous CV problems, conditions that predispose the patient to develop CVD(i.e., HTN, hyperlipidemia, or DM, heart murmurs, congenital heart disease, rheumatic fever or unexplained joint pains), or comorbid conditions that influence the identification or management of CVD.
- The patient should be asked about social habits that affect the CVS, including diet, amount of regular physical activity, tobacco use, alcohol intake, & illicit drug use.
  - At present, family Hx is the best available screening tool to identify patients with a genetic predisposition for CVD.

TABLE 17-1 Risk Factors for Cardiovascular Disease
Non-Modifiable
Advancing age
Male
Family history of early onset CVD
Postmenopausal status
Modifiable
Hypertension
Diabetes mellitus
Dyslipidemia
Cigarette smoking
Obesity
Physical inactivity
Excessive alcohol
Stress
Chronic inflammation (i.e., gingivitis, arthritis, elevated C-reactive protein, etc.) Illicit drug use (e.g., cocaine or methamphetamine)

Cardiovascular History

- **Chest Pain**
  - Is a frequent symptom & may occur as a result of myocardial ischemia (angina pectoris) or infarction or a variety of noncardiac conditions(esophageal, pulmonary, or musculoskeletal disorders).
  - The quality of chest pain, its location & duration, & the factors that provoke or relieve it are important in ascertaining its etiology.
- **Angina pain-** a sensation of heaviness or pressure in the retrosternal area that may radiate to the jaw, left shoulder, back, or left arm. It typically lasts only a few minutes. It is precipitated by exertion, emotional stress, eating, smoking a cigarette, or exposure to cold, & it is usually relieved with rest or a sublingual nitroglycerin, although the latter also is effective in relieving chest pain due to esophageal spasm.
  - **Angina** that is increasing in severity, longer in duration, or occurring at rest is called unstable angina; it should prompt the patient to seek medical attention expeditiously.

CV Hx…

- The patient with CHF & pulmonary vascular congestion may complain of SOB (dyspnea) with exertion or even at rest, orthopnea, paroxysmal nocturnal dyspnea, & nocturia.
- The patient with CHF & peripheral venous congestion may report abdominal swelling (from hepatic congestion or ascites), nausea, vomiting, lower extremity edema, fatigue, & dyspnea.
- NYHA grading system is used to indicate whether a patient has angina or symptoms of CHF with vigorous (Class I), moderate (Class II), mild (Class III), or minimal/no (Class IV) exertion.

Physical Examination

- The patient with suspected heart disease should undergo a comprehensive physical examination, with particular attention to the CVS.
- This should include an assessment of the jugular venous pulse, carotid & peripheral arterial pulses, examination of the heart & lungs (i.e., palpation, percussion, & auscultation), & inspection of the abdomen & extremities.

Jugular Venous Pressure

- JVP is an indirect assessment of right atrial pressure.
- With the patient lying supine at 30 degrees & his/her head rotated slightly to the left, the height of the fluid wave in the right internal jugular vein is determined relative to the sternal angle.
- The normal JVP is 1 to 2 cm above the sternal angle. The JVP typically is elevated in the patient with heart failure.
- The extent of elevation can be used to assess the severity of peripheral venous congestion, & its diminution can be used to assess the response to therapy.

Arterial Pulses

- The carotid arterial pulse is examined for its intensity &, concurrently with the apical impulse, for concordance within the cardiac cycle.
- Diminished carotid arterial pulsations may be the result of a reduced stroke volume, atherosclerotic narrowing of the carotid artery, or obstruction to left ventricular outflow, as may occur with aortic valve stenosis or hypertrophic obstructive cardiomyopathy.
- Conversely, very forceful, hyperdynamic, "bounding" carotid arterial pulsations may be palpated in the patient with an increased stroke volume & suggests the presence of chronic aortic valve regurgitation or a high cardiac output due, for example, to hyperthyroidism, an arteriovenous shunt, or marked anemia.

Arterial Pulses…

- The pulses in the arms & legs also are examined.
  - Diminished peripheral pulses suggest the presence of a reduced stroke volume or atherosclerotic peripheral arterial disease (PAD).
- Concomitant pallor, skin atrophy, hair loss, or ulcerations is consistent with PAD, which often coexists with coronary artery disease.
- To quantify the severity of PAD, systolic arterial pressure is measured in all four extremities.
  - Normally, the systolic arterial pressure in the feet should be similar or even slightly higher than the pressure in the arms.
- Thus, the ratio of the systolic arterial pressures in the foot & arm (the so-called ankle-brachial index [ABI]) is normally >1.0.
  - An ABI <0.9 suggests PAD.

Chest

- In the patient with chest pain, a thorough lung examination should be performed to exclude a pulmonary cause.
- The anterior chest wall is palpated to assess for the presence of tenderness in the sternal area, which may indicate that the patient has costochondritis.
- Percussion of the posterior chest is done to determine if a pleural effusion is present.
- Auscultation of the anterior & posterior lung fields is performed to assess for the presence of findings suggestive of pneumonia, airway obstruction, pleural effusion, or pulmonary edema.

Heart Sounds

- The typical "lub-dub" sound of the normal heart consists of;
  - The first heart sound (**S_1**), which precedes ventricular contraction & is due to closure of the mitral & tricuspid valves, &
  - The second heart sound (**S_2**), which follows ventricular contraction & is due to closure of the aortic & pulmonic valves.
- Other heart sounds, which are normally not present (i.e., a third heart sound (S_3), fourth heart sound (S_4), or murmur), may indicate the presence of underlying heart disease.

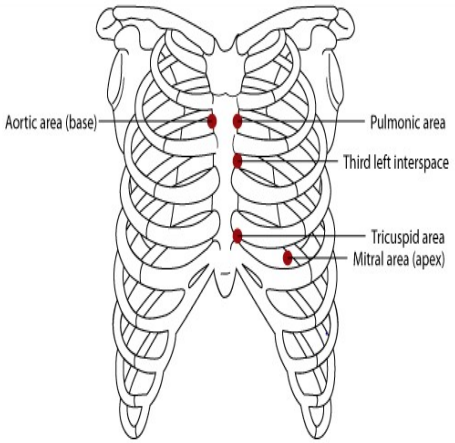
Heart Sounds…

- The **S_3**, a so-called ventricular gallop, is a low-pitched sound usually heard at cardiac apex in early diastole *(i.e., immediately after S_2)*.
- It is caused by the vibrations that occur when blood rapidly rushes from a "tense" atrium into a stiff, noncompliant ventricle.
  - Thus, it is usually associated with decompensated CHF or intravascular volume overload. A so-called "physiologic" S_3 is heard commonly in healthy children & may persist into young adulthood.
- The **S_4** is a dull, low-pitched sound that is caused by the vibrations that occur when atrial contraction forces blood into a stiff, noncompliant ventricle. It is audible at the cardiac apex just before ventricular contraction (i.e., just before S_1); it is not present in the subject with a normal heart.
  - An S_4 may be present in the patient with aortic stenosis, systemic arterial HTN, hypertrophic cardiomyopathy, or coronary artery disease.

Heart Sounds…

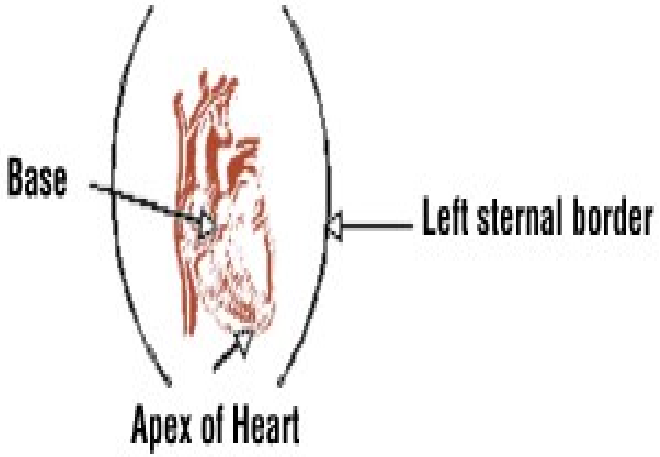
- Murmurs are auditory vibrations resulting from turbulent blood flow within the heart chambers or across the valves.
- They are classified by their timing & duration within the cardiac cycle (systolic, diastolic, or continuous), location on the chest wall, intensity (grade 1 to 6, from softest to loudest), pitch (high or low frequency), & radiation.
- Some murmurs are said to be "innocent" or "physiologic" & result from rapid, turbulent blood flow in the absence of cardiac disease.
  - Fever, anxiety, anemia, hyperthyroidism, & pregnancy increase the intensity of a physiologic murmur.

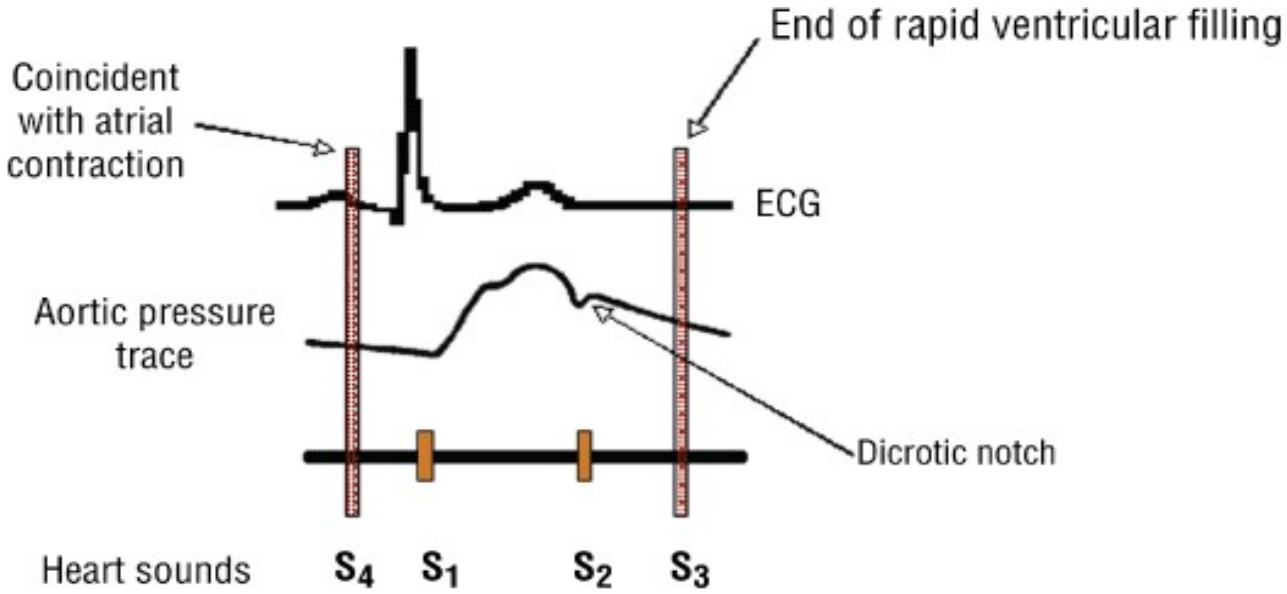
Figure 17-2.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

Schematic illustrations of topographic areas on the precordium for cardiac auscultation. Auscultatory areas do not correspond to anatomic locations of the valves but to the sites at which particular valves are heard best. *(Redrawn from Kinney MR, Packa DR, eds. Andreoli's Comprehensive Cardiac Care, 8th ed. St. Louis, MO: Mosby, 1996, with permission.)*





Heart Sounds…

- Systolic murmurs occur during ventricular contraction. They begin with or after S_1 & end at or before S_2, depending on the origin of the murmur.
  - They are classified based on time of onset & termination within systole: midsystolic or holosystolic (pansystolic).
  - Examples of midsystolic murmurs include pulmonic stenosis, aortic stenosis, & hypertrophic obstructive cardiomyopathy.
  - Holosystolic murmurs occur when blood flows from a chamber of higher pressure to one of lower pressure throughout systole, such as occurs with mitral or tricuspid valve regurgitation or a ventricular septal defect.

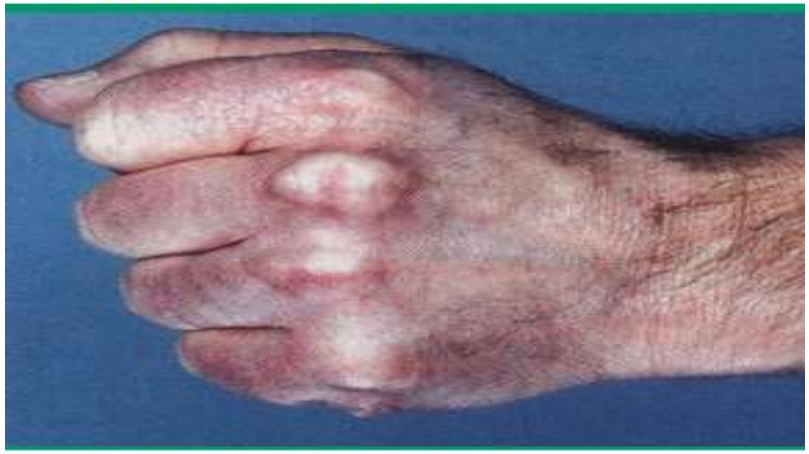
Heart Sounds…

- Diastolic murmurs occur during ventricular filling. They begin with or after S_2, depending on the origin of the murmur. Aortic or pulmonic valve regurgitation causes a high-pitched diastolic murmur that begins with S_2, whereas stenosis of the mitral or tricuspid valves causes a low-pitched, "rumbling" diastolic murmur.
- **Continuous murmurs** begin in systole & continue without interruption into all or part of diastole. Such murmurs are mainly a result of aortopulmonary connections (e.g., patent ductus arteriosus) or arteriovenous connections (e.g., arteriovenous fistula, coronary artery fistula, or arteriovenous malformation).
  - When a murmur is heard, the cardiac abnormality underlying it usually can be confirmed & assessed with echocardiography or other imaging modalities, such as cardiac angiography or MRI.

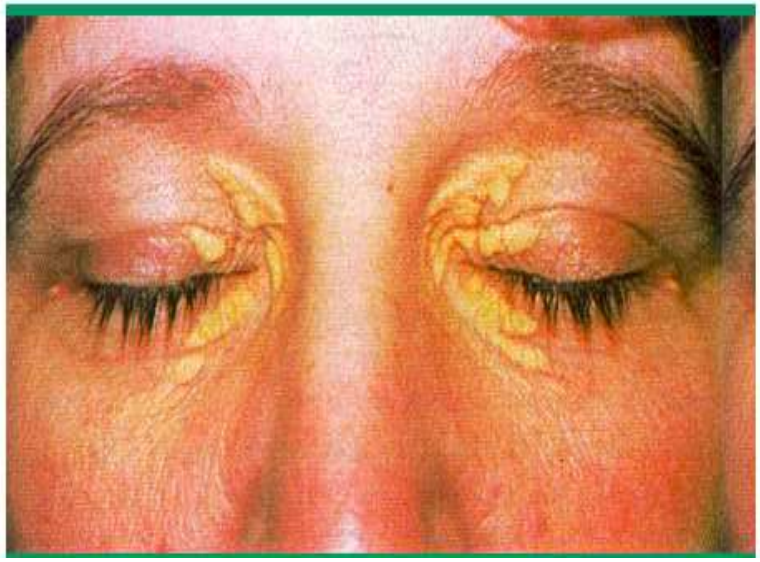
Inspection

- **General Appearance**
  - Is the patient in acute distress?
  - Is breathing labored or easy?
  - Is there use of accessory muscles?
  - Is there cyanosis? Pallor?
- Are **xanthomata** present (stony hard, yellowish masses on extensor tendons of the fingers.
  - Due to hypercholesterolemia
- Inspect eyes-Yellow plaques on eyelids
  - **Xanthelasma** may be due to hyperlipoproteinemia
- Inspect nails- Splinter hemorrhages are associated with infective endocarditis

Tendon xanthomata



Xanthelasma



Splinter hemorrhages in infective endocarditis

Inspection Of The Extremities

- Look for edema (pitting & non-pitting)
- Observe color
- Babies with atrial septal defects may have an extra finger or toe.
- Loss of hair may indicate PVD.

Assessment of Blood Pressure

- Always measure in both arms sitting
- Then take BP standing

Orthostatic Hypotension

- Have the patient lie down for 5 minutes & measure BP & pulse
- Have patient stand & repeat reading immediately. Allow 90 seconds for maximum orthostatic changes
  - **A drop in systolic BP of 20 mmHg or more when standing is orthostatic.**
- There is usually an increase in HR.

Assessment of the Arterial Pulse

- Grasp both radial arteries, count for 30 seconds, & multiply by 2.
- Determine rhythm.
- If the rhythm is irregular, is there a pattern to the irregularity?
- A grossly irregular rhythm is most likely atrial fibrillation
- Palpate the carotid artery by standing at the patients' right side with him resting on his back
- Never palpate both carotids at the same time

Percussion

- Not helpful in CV assessment
- CXR shows heart size & borders very accurately

Palpation

Point of Maximal Impulse (PMI)

- Stand on the right side of the patient with him sitting. Place fingertips at 5th ICS, MCL & you should feel PMI.
- PMI is usually within 10 cm of the midsternal line & no larger than 2-3 cm diameter
- PMI that is lateral or displaced suggests cardiomegaly.
- About 70% of the time you will be able to feel PMI with patient sitting. If you can't, turn patient to his left side, lying down.
- A PMI that is over 3 cm diameter indicates left ventricular hypertrophy & is 86% predictive of increased left ventricular end diastolic pressure.

"Have you ever felt a thrill?"

- Thrills are superficial vibratory sensations felt on the skin overlying an area of turbulence.
- The presence of a thrill indicates that you will hear a loud murmur.
- Simply an indication of what you will hear when you listen.

Auscultation

General Principles

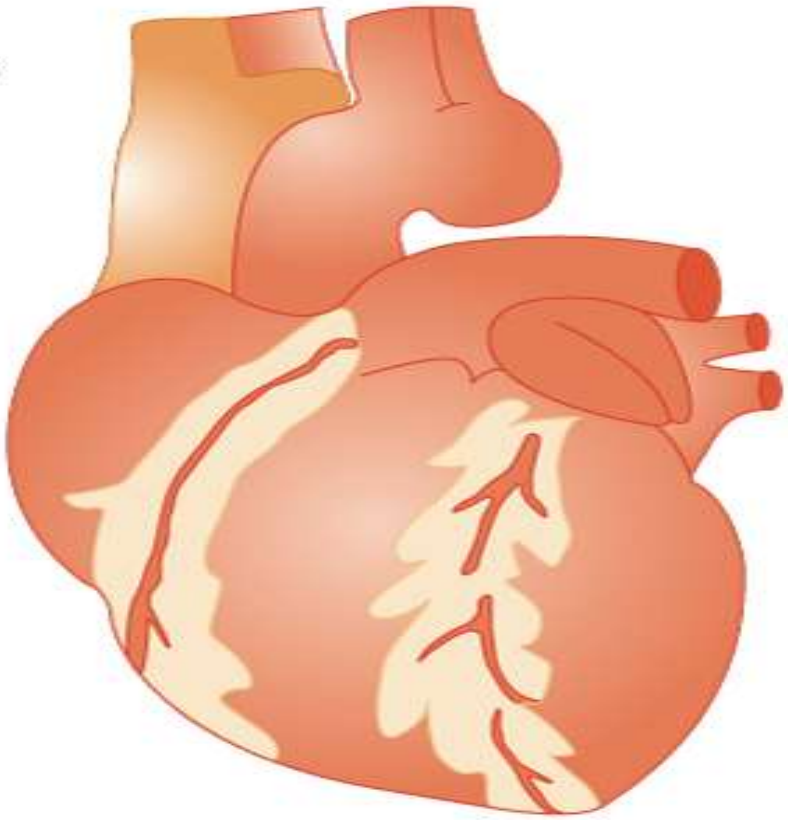
- Close your eyes when listening
- Never listen through any kind of clothing
- Listen at all 4 cardiac areas:
  - Aortic --2nd ICS, RSB
  - Pulmonic---2nd ICS, LSB
  - Mitral--Cardiac apex, 5th ICS, MCL
  - Tricuspid---Left lower sternal border
- Normally only the closing of valves can be heard.
- Closure of the tricuspid & mitral valves (AV valves) produce the 1st heart sound.
- Closure of the aortic & pulmonic valves produce the 2nd heart sound.
- Opening of valves can only be heard if they are very damaged (opening "snap" "click").

Laboratory Testing Modalities

Figure 17-4.

Cardiac Biomarkers

Markers of myonecrosis
- Cardiac troponin (cTn)
- Creatine kinase MB (CK-MB)
- Myoglobin



Markers of inflammation
- C reactive protein (CRP)
- Myeloperoxidase
- P-selectin
- CD40 ligand
- Interleukin
- Fibrinogen

Markers of hemodynamic stress
- B-type natriuretic peptide (BNP)
- N-terminal pro BNP (NT-proBNP)

Cardiac Isoenzymes

- Total CK (Creatine Kinase)
  - Enzyme found in heart, skeletal, & brain muscle cells. Enzyme is released with injury to cells
  - Increases with acute MI, myocarditis, post-CABG, cardioversion(defibrillation)
  - Can also elevate with rhabdomyolysis. May see with cocaine intoxication & adverse effect from statin drugs for hypercholestolemia
- CK-MB
  - Specific to myocardium
  - Increases with acute MI, myocarditis , post-CABG, cardioversion
  - May also elevate with chronic renal failure
  - With acute MI, MB occurs in serum in 6-12 hrs. & remains for 18-32 hrs.
  - Presence is diagnostic of MI.

Cardiac Isoenzymes

- MB Index
  - Percentage of MB in comparison with total CK
- *** Three sets of cardiac isoenzymes should be ordered 8 hrs. apart to diagnose/confirm acute MI.

Troponin I & T

Troponin I

- More specific
- Unique to heart muscle
- Released with very small amounts of damage as early as 1-3 hrs. after injury
- Peaks in 12-48 hrs.
- Levels return to normal in 7-10 days.
- Useful in delayed Dx of MI also

Troponin T

- May also elevate in unstable angina, myocarditis, chronic renal failure, acute muscle trauma, rhabdomyolysis, polymyositis, & dermatomyosis.

Myoglobin

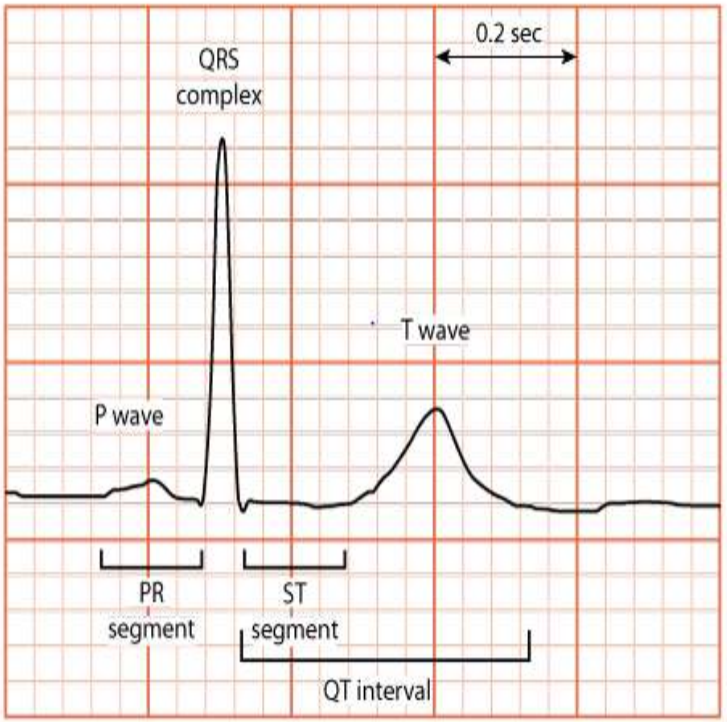
- Oxygen-binding protein of striated muscle.
  - Released with injury to muscle.
- Used as early marker of muscle damage in MI.
- Elevates in 2-4 hrs.
- Peaks in 8-10 hrs.
- Returns to normal in 24 hrs.

B-type Natriuretic Peptide (BNP)

- Hormone produced by ventricles of the heart that increases in response to ventricular volume expansion & pressure overload.
- Marker of ventricular systolic & diastolic dysfunction
- Useful in diagnosing CHF
- Normal is less than 100 ng/L

Electrocardiography

Figure 17-10.



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ECG waveforms are labeled alphabetically and are read from left to right. The *P wave* represents depolarization of the atria. The *PR segment* is created by passage of the impulse through the atrioventricular node and the bundle of His and its branches. The *QRS complex* represents electrical depolarization of the ventricles. The *T wave* results from ventricular depolarization. A plateau phase called the *ST segment* extends from the end of the QRS complex to the beginning of the T wave. The ST segment elevates with infarction and depresses with ischemia. The *QT interval*—measured from the beginning of the QRS complex to the end of the T wave—includes the time required for ventricular depolarization and repolarization.

ELECTROCARDIOGRAM(EKG or ECG)

- Cardiac rhythm
- Chamber enlargement
- Conduction abnormalities
- Electrolyte & toxic disorders
  - Peaked T-waves = Hyperkalemia
  - U waves = Hypokalemia
  - QT prolongation = Toxic drug effects
- Acute MI
  - T wave inversion = Ischemia
  - ST elevation = Acute injury
  - Q waves = Transmural MI
  - Can have an mi with normal EKG!!

Chest X-ray (CXR)

- Heart size
- Calcification on valves & arteries
- Evidence of CHF
  - Pulmonary vascular congestion
  - Pleural effusions
- Masses

Echocardiogram(ECHO)

- Structural Abnormalities
  - Anatomical
  - Presence of thrombi, vegetations,
  - Presence of pericardial effusion
- Chamber sizes
- Valvular function
- Left ventricular function
  - Wall motion, Ejection Fraction (EF)

Stress Testing

- Exercise Treadmill testing/ Exercise Tolerance Test
  - Test would be indicative of CAD on the development of angina, ECG signs of ischemia, arrhythmias, abnormal heart rate, or abnormal BP response.
- Stress Echocardiogram
  - Types – Exercise, Dobutamine
- All are done mainly to evaluate myocardial ischemia.

Radionuclide Angiography

- Often called MUGA scan – Stands for multiple gated angiography
- Determines ejection fraction
- Almost always automatically done with MRI now

Computed Tomography (CT)

- Helical CT
  - Uses IV Contrast
  - Used to diagnose Aortic dissection, Pulmonary emboli
- Plain CT
  - Abnormal masses (with or without contrast)
  - Hematoma or retroperitoneal bleed – better with IV contrast
- Ultrafast CT
  - No contrast used
  - Detection of coronary artery calcification as indicator of atherosclerosis
  - The higher the score, the more calcium detected.

Cardiac Catheterization

- Uses IV contrast
- Reveals:
  - Pressures in chambers/Aorta
  - LV wall motion & ejection fraction
  - Visualization of coronary anatomy
  - Valvular function

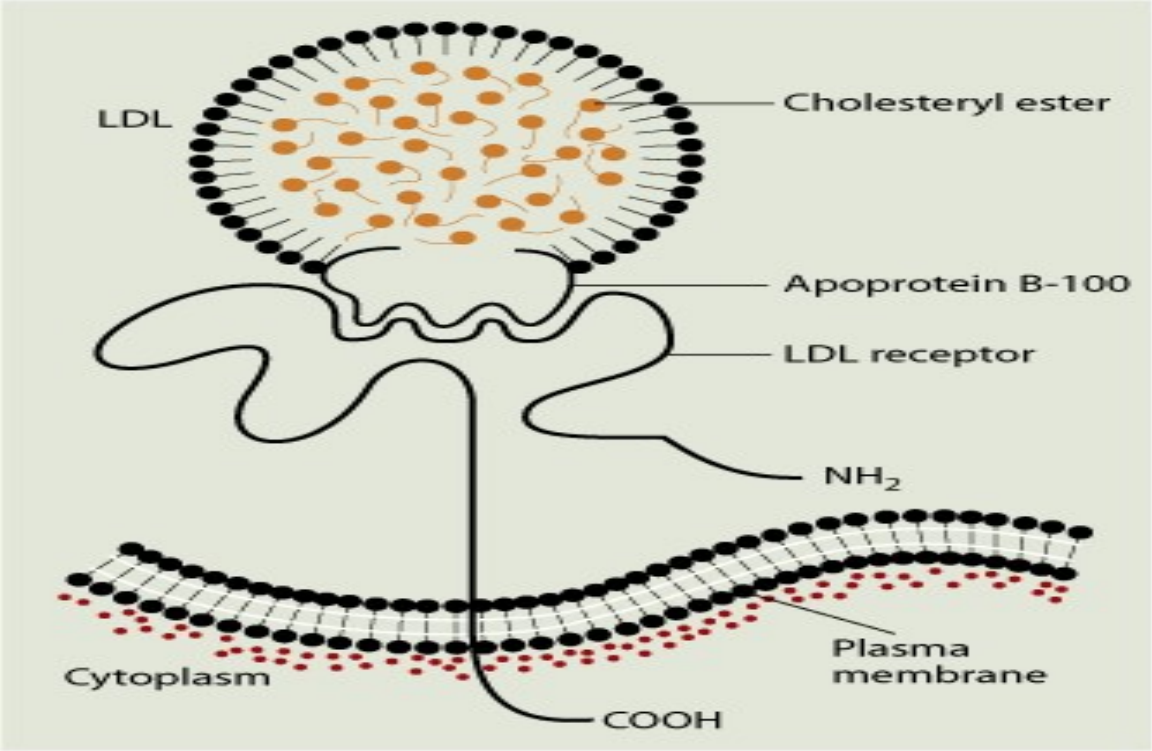
Ventilation-Perfusion Scan(V/Q Scan)

- Used to diagnose Pulmonary embolism
- Will read as high, moderate, or low probability for PE.

Summary

- A careful patient Hx and physical examination are extremely important in diagnosing cardiovascular disease and should be done prior to any test.
- Heart sounds and heart murmurs are important in identifying heart valve abnormalities and other structural cardiac defects.
- Elevated jugular venous pressure is an important sign of heart failure and may be used to assess severity and response to therapy.
- Electrocardiography is useful for determining rhythm disturbances (tachy- or bradyarrhythmias).
- Exercise stress testing provides important information concerning the likelihood and severity of coronary artery disease; changes in the electrocardiogram, blood pressure, and heart rate are used to assess the response to exercise.
- Cardiac catheterization and angiography are used to assess coronary anatomy and ventricular performance.
- Echocardiography is used to assess valve structure and function as well as ventricular wall motion; transesophogeal echocardiography is more sensitive for detecting thrombus and vegetations than transthoracic echocardiography.
- Radionuclides such as technetium-99m and thallium-201 are used to assess ischemia and myocardial viability with suspected coronary artery disease and heart failure.
- Pharmacologic stress testing is used when patients cannot perform physical exercise to assess the likelihood of coronary artery disease.

Dyslipidemia



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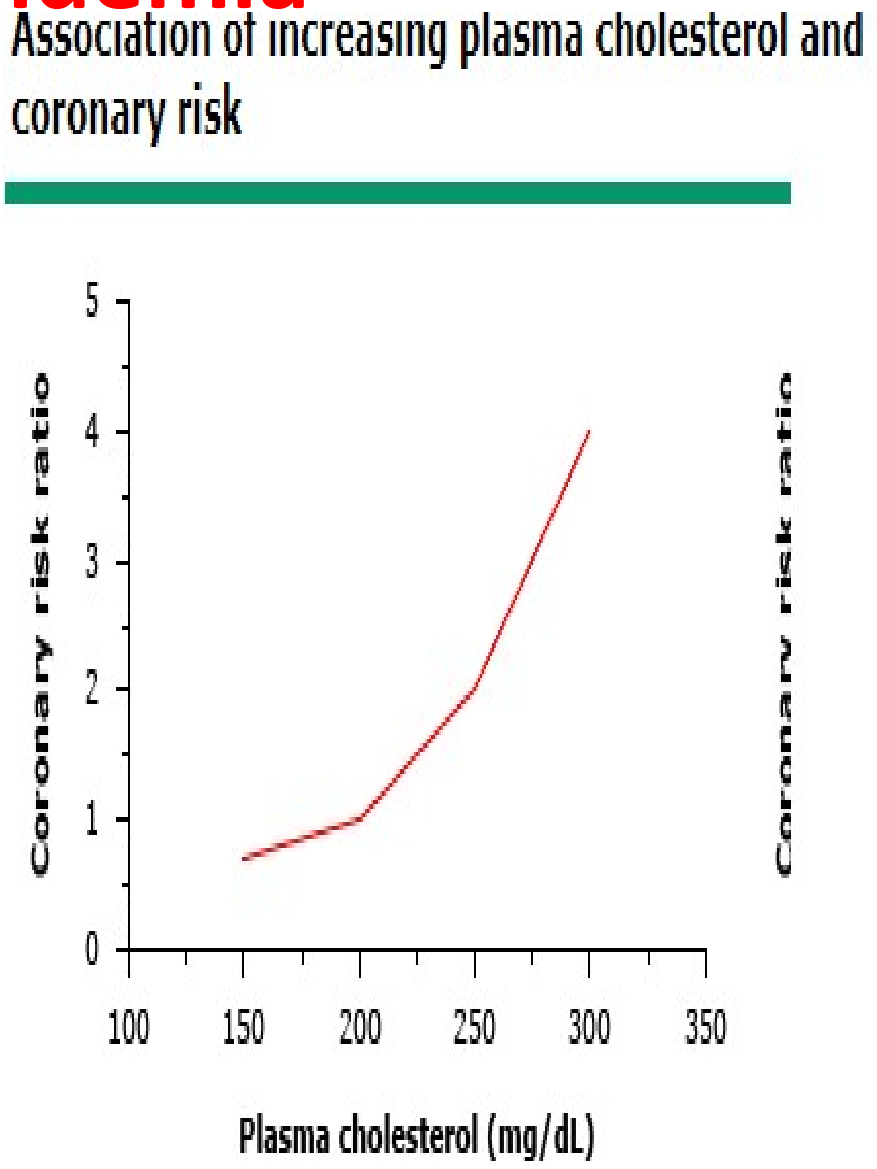
Learning Objectives

- Upon completion of this session, the students will be able to:
  - Identify the common types of lipid disorders.
  - Identify the statin-benefit groups and intensity of statin therapy
  - Recommend appropriate therapeutic lifestyle changes (TLC) and pharmacotherapy interventions for dyslipidemia.
  - Determine a patient's atherosclerotic CV disease risk and corresponding treatment goals
  - Identify diagnostic criteria and treatment strategies for metabolic syndrome.
  - Describe components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for dyslipidemias.
  - Educate patients about the disease state, appropriate TLC, and drug therapy required for effective treatment.

Hyperlipidemia

- Elevated blood levels of lipoproteins (cholesterol, triglycerides, phospholipids)
- Lipoprotein abnormalities: ≥ 1 of the following
  - Elevated total cholesterol (TC)
  - Elevated low-density lipoprotein (LDL)
  - Elevated triglycerides (TG)
  - Reduced high-density lipoprotein (HDL)
- CHD risk directly correlates with TC & LDL levels in graded, continuous fashion.
- > 50% of American adults: total cholesterol ≥ 200 mg/dL
- < 50% of patients with established CHD are receiving lipid lowering treatment
- Lipid lowering drug therapy reduces risk of CV/cerebrovascular events, death.



Hyperlipidemia

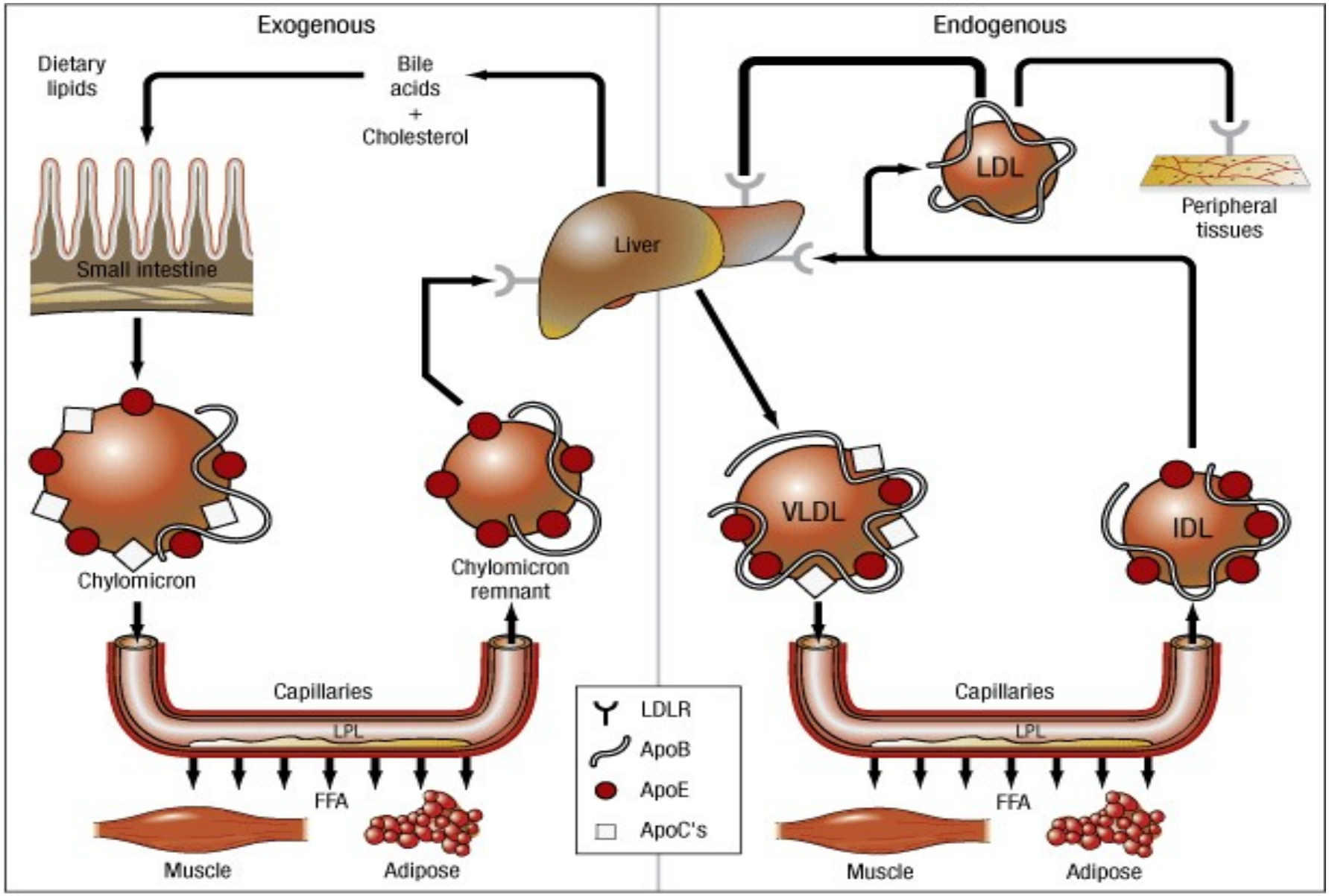
- Hypercholesterolemia additive to nonlipid CHD risk factors: cigarette smoking, HTN, DM, low HDL, electrocardiographic abnormalities
- Presence of CHD, prior MI increases MI risk 5 to 7 times.
- LDL level: significant predictor of morbidity/mortality
- ~50% of MIs and $\geq$ 70% of CHD deaths occur in patients with known CHD.

Background & Pathophysiology

- Cholesterol: essential for cell membrane formation & hormone synthesis.
- Lipids not present in free form in plasma; circulate as lipoproteins
- 3 major plasma lipoproteins:
  - VLDL carries ~10 to 15 % of total serum cholesterol; carried in circulation as TG; VLDL = TG/5.
  - LDL carries 60 to 70% of total serum cholesterol; IDL is also included in this group.
  - HDL carries 20 to 30% of total serum cholesterol; reverse transportation of cholesterol.
- VLDL secreted from the liver
  - Converted to IDL then LDL.
- Plasma LDL taken up by receptors on liver, adrenal, & peripheral cells
  - Recognize LDL apolipoprotein B-100.

Background & Pathophysiology…

- LDL internalized & degraded by these cells
- Increased intracellular cholesterol levels inhibits HMG-CoA reductase & decreases LDL receptor synthesis.
- Decreases in LDL receptors: plasma LDL not as readily taken up & broken down by cells.
- LDL also excreted in bile
  - Joins enterohepatic pool
  - Eliminated in stool
  - Can be oxidized in subendothelial space of arteries
- Oxidized LDL in artery walls provokes inflammatory response
- Monocytes recruited & transformed into macrophages
  - Results in cholesterol laden foam cell accumulation
- Foam cells: beginning of arterial fatty streak
- If processes continue: angina, stroke, MI, peripheral artery disease, arrhythmias, death.



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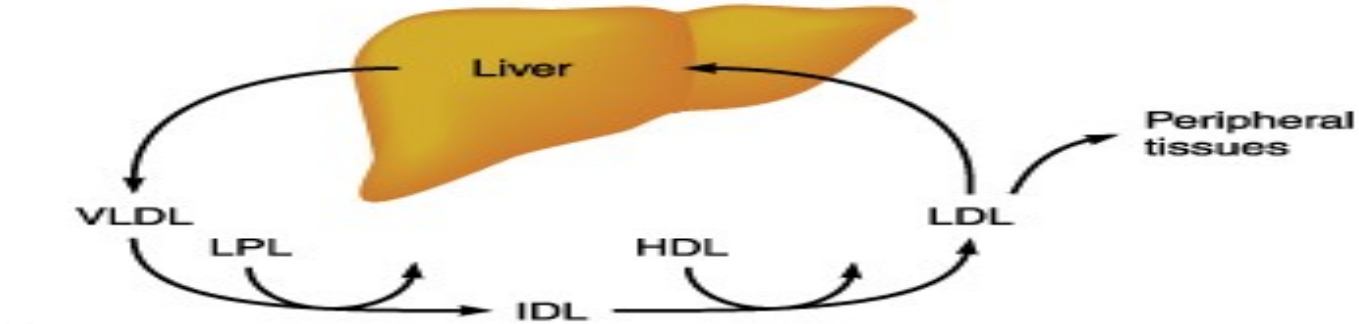

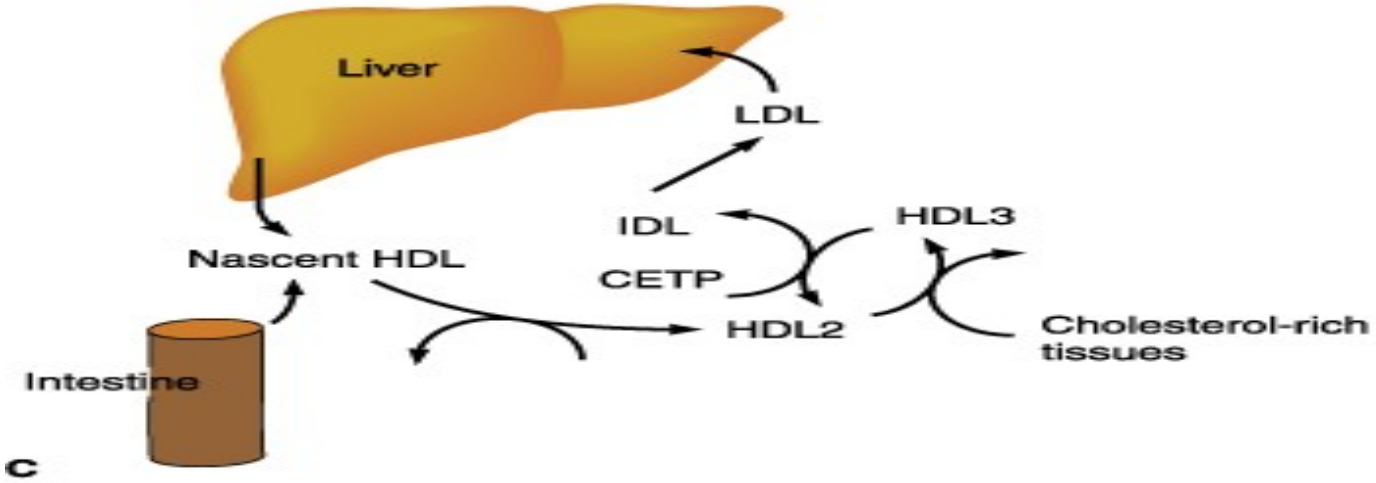

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Etiology

- Lipoprotein disorders: 6 categories based on phenotype
- Specific genetic defects with disrupted protein, cell, and organ function give rise to several disorders within each family of lipoproteins.
- Elevated cholesterol: not necessarily familial hypercholesterolemia (type IIa).
  - Cholesterol may be elevated in other lipoprotein disorders
  - Lipoprotein pattern does not describe underlying genetic defect
- Many genetic abnormalities & environmental factors lead to lipoprotein abnormalities.
- Current laboratory values can not define underlying abnormality.
- 2˚ hyperlipidemia should be initially managed by correcting underlying abnormality when possible.

Hyperlipoproteinemia Classification

Fredrickson-Levy-Lees Classification

Type	Lipoprotein Elevation
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL (LDL_1)
IV	VLDL
V	VLDL + Chylomicrons

IDL, intermediate-density lipoprotein
LDL, low-density lipoprotein
VLDL, very-low-density lipoprotein

Lipid Phenotype	Plasma Lipid Levels [mmol/L (mg/dL)]	Lipoprotein Elevated	Phenotype	Clinical Signs
Isolated hypercholesterolemia				
Familial hypercholesterolemia	Heterozygotes TC = 7–13 (275–500)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease at 30–50 years
	Homozygotes TC >13 (>500)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease in childhood
Familial defective Apo B-100	Heterozygotes TC = 7–13 (275–500)	LDL	IIa	
Polygenic hypercholesterolemia	TC = 6.5–9 (250–350)	LDL	IIa	Usually asymptomatic until vascular disease develops; no xanthomas
Isolated hypertriglyceridemia				
Familial hypertriglyceridemia	TG = 2.8–8.5 (250–750)	VLDL	IV	Asymptomatic; may be associated with increased risk of vascular disease
Familial LPL deficiency	TG >8.5 (750)	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitis, abdominal pain, hepatosplenomegaly
Familial Apo C-II deficiency	TG >8.5 (>750)	Chylomicrons, VLDL	I, V	As above

Lipid Phenotype	Plasma Lipid Levels [mmol/L (mg/dL)]	Lipoprotein Elevated	Phenotype	Clinical Signs
Hypertriglyceridemia and hypercholesterolemia				
Combined hyperlipidemia	TG = 2.8–8.5 (250–750); TC = 6.5–13 (250–500)	VLDL, LDL	IIb	Usually asymptomatic until vascular disease develops; familial form may present as isolated high TG or isolated high LDL cholesterol
Dysbetalipo-proteinemia	TG = 2.8–8.5 (250–750); TC = 6.5–13 (250–500)	VLDL, IDL; LDL normal	III	Usually asymptomatic until vascular disease develops; may have palmar or tuboeruptive xanthomas

Lipoprotein Abnormalities: 2˚ Causes

- Hypercholesterolemia
  - Hypothyroidism
  - Obstructive Liver Disease
  - Nephrotic Syndrome
  - Anorexia Nervosa
  - Acute Intermittent Porphyria
  - Medications
    - » Progestins
    - » Thiazide Diuretics
    - » Glucocorticoids
    - » B-blockers
    - » Isotretinoin
    - » Protease Inhibitors
    - » Cyclosporine
    - » Mirtazipine
    - » Sirolimus

Lipoprotein Abnormalities: 2˚ Causes

- Hypertriglyceridemia
  - Obesity
  - Dm
  - Lipodystrophy
  - Glycogen Storage Disease
  - Ileal Bypass Surgery
  - Sepsis
  - Pregnancy
  - Monocolonal Gammopathy: Multiple Myeloma, Lymphoma
  - Acute Hepatitis
  - Systemic Lupus Erythematous

- Medications
  - Alcohol
  - Estrogens
  - Isotretinoin
  - B-blockers
  - Glucocorticoids
  - Bile Acid Resins
  - Thiazides
  - Asparaginase
  - Interferons
  - Azole Antifungals
  - Mirtazipine
  - Anabolic Steroids
  - Sirolimus

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Lipoprotein Abnormalities: 2˚ Causes

- Hypocholesterolemia
  - Malnutrition
  - Malabsorption
  - Myeloproliferative Diseases
  - Chronic Infectious Diseases
    - Acquired Immune Deficiency Syndrome
    - Tuberculosis
  - Monoclonal Gammopathy
  - Chronic Liver Disease
- Low HDL
  - Malnutrition
  - Obesity
  - Medications
    - Non-ISA B-blockers
    - Anabolic Steroids
    - Isotretinoin
    - Progestins

Clinical Presentation

- Most patients asymptomatic for years before disease is clinically evident
- Metabolic syndrome: ≥ 3 of the following
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Increased BP
  - Insulin resistance ± glucose intolerance
  - Prothrombotic state
  - Proinflammatory state

Clinical Presentation

- **Symptoms:**
  - None
  - Severe chest pain, palpitations
  - Sweating
  - Anxiety
  - SOB
  - Loss of consciousness
  - speech or movement difficulty
  - abdominal pain
  - sudden death
- **Signs**
  - None
  - Severe abdominal pain
  - Pancreatitis
  - eruptive xanthomas
  - Peripheral polyneuropathy
  - HTN
  - BMI > 30 kg/m^2
  - waist size > 40 in (men), > 35 in (women)

Lab Tests:

- ↑ TC
- ↑ LDL
- ↑ TG
- ↑ apolipoprotein B
- ↑ C-reactive protein
- ↓ HDL

Patient Evaluation

- Fasting lipid panel every 5 yrs adults > 20 years
  - If patient not fasting only TC & HDL are reliable
  - TC > 200 or HDL < 40: obtain follow-up fasting lipid panel
- Once lipoprotein abnormality confirmed; assess health & CV risk factors
- Initiate individualized LDL goals & treatment
- If the triglyceride levels are below 400 mg/dL
- Then one can calculate VLDL and LDL concentrations:
- VLDL = triglyceride/5
- LDL = total cholesterol – (VLDL + HDL).

Classification

Total cholesterol	
<200	Desirable
200–239	Borderline high
240	High
LDL cholesterol	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
190	Very high
HDL cholesterol	
<40	Low
60 mg/dL	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
500	Very high

All values are mg/dL

Risk Factors[a]

Age
Men: 45 years
Women: 55 years or premature menopause without estrogen replacement therapy
Family history of premature CHD (definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative)
Cigarette smoking
Hypertension (140/90 mm Hg or taking antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)[b]

[a]Diabetes regarded as coronary heart disease (CHD) risk equivalent.
[b]HDL cholesterol ≥60 mg/dL counts as "negative" risk factor; its presence removes one risk factor from the total count.

Treatment Goals

- LDL: predicts morbidity, mortality
  - 1˚ treatment target
- More CHD risk factors or higher Framingham Global Risk Score: more stringent LDL goal

Goals & Cutpoints

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	100	100 (<100 mg/dL; consider drug options)[a]
Moderately high risk: 2+ risk factors (10-year risk >10%–20%)	<130	130	130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	130	160
Lower risk: 0–1 risk factor[b]	<160	160	190 (160–189: LDL-lowering drug optional)

[a]Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes (TLC). Others prefer to use drugs that primarily modify triglycerides and high-density lipoprotein, e.g., nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory.

[b]Almost all people with 0–1 risk factor have a 10-year risk <10%; thus,10-year risk assessment in people with 0–1 risk factor is not necessary.

Non-pharmacologic Therapy

- Initial treatment for any lipoprotein disorder is TLC (Therapeutic Lifestyle Changes)
  - Restricted total fats, saturated fats, cholesterol intake
  - Modest increase in polyunsaturated fat
  - Increased soluble fiber intake
  - Exercise: moderate intensity 30 min/day most days
    - caution in high risk patients or those with CAD
  - Weight reduction (initial goal of 10%) if needed
  - Smoking cessation
  - Treat HTN

TLC Dietary Recommendations

Component[a]	Recommended Intake
Total fat	25% to 35% of total calories
Saturated fat	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates[b]	50% to 60% of total calories
Cholesterol	< 200 mg/day
Dietary fiber	20 to 30 g/day
Plant sterols	2 g/day
Protein	~15% of total calories
Total calories	To achieve & maintain desirable body weight

[a]Calories from alcohol not included.
[b]Complex carbohydrates (whole grains, fruits, vegetables).

Pharmacologic Therapy

- Most patients should receive 3 month TLC trial before initiating pharmacologic therapy unless very high risk
- If patient unable to reach goals with TLC alone choose lipid-lowering drugs based on lipoprotein disorder
- Combination therapy may be necessary
  - Monitor closely: increased risk of drug interactions, adverse effects

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins	Comment
Cholestyramine, colestipol, colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓Cholesterol	↓ LDL ↓ VLDL	Problem with compliance; binds many coadministered acidic drugs
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓Cholesterol	↓ VLDL ↓ LDL ↑ HDL	Problems with patient acceptance; good in combination with bile acid resins; ER niacin causes less flushing and is less hepatotoxic than SR form
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓Cholesterol	↓ VLDL ↓ LDL ↑ HDL	Clofibrate causes cholesterol gallstones; modest LDL lowering; raises HDL; gemfibrozil inhibits glucuronidation of simvastatin, lovastatin, atorvastatin
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism; inhibit LDL synthesis	↓Cholesterol	↓ LDL	Highly effective in heterozygous familial hypercholesterolemia and in combination with other agents
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓Cholesterol	↓ LDL	Few adverse effects; effects additive to other drugs; ENHANCE trial – no change in carotid intima media thickness (CIMT) compared to simvastatin monotherapy in patients with familial hypercholesterolemia

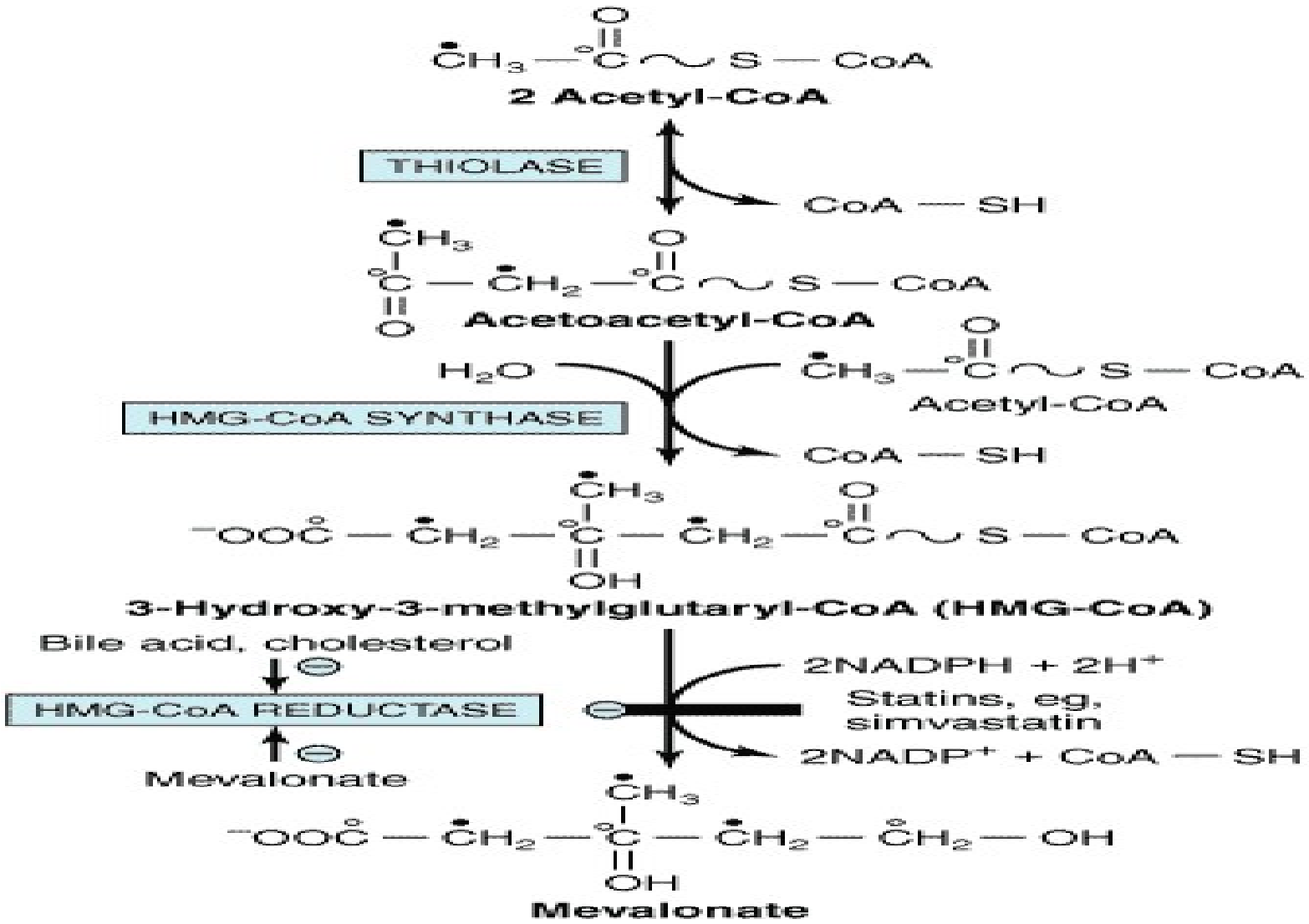
Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	—
IIa	Statins Cholestyramine or colestipol Niacin	Niacin, BAR Statins, niacin Statins, BAR Ezetimibe
IIb	Statins Fibrates Niacin	BAR, fibrates,[b] niacin Statins, niacin, BAR[a] Statins, fibrates Ezetimibe
III	Fibrates Niacin	Statins niacin Statins fibrates Ezetimibe
IV	Fibrates Niacin	Niacin Fibrates
V	Fibrates Niacin	Niacin Fish oils

[a]Bile acid resins (BARs) not 1st line if TGs are elevated at baseline; hypertriglyceridemia may worsen with BAR monotherapy. [b]Fibrates: gemfibrozil, fenofibrate

HMG-CoA Reductase Inhibitors

- Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
- Inhibit HMG-CoA conversion to mevalonate.
  - Rate limiting step in cholesterol synthesis
- Most potent TC/LDL lowering agents
- Dose dependent decrease in TC/LDL
  - averages > 30% when used with dietary therapy
- Short t½ except atorvastatin, rosuvastatin
  - may account for higher atorvastatin & rosuvastatin potency
- Dosed once daily in evening
  - hepatic cholesterol production peaks at night
  - exceptions: atorvastatin, rosuvastatin
- Rosuvastatin requires dosage adjustment in severe renal impairment & hepatic disease
- Good compliance rate, low incidence of adverse effects
- Adverse effects:
  - Elevated serum transaminases, myalgia, myopathy, rhabdomyolysis, flu-like symptoms, mild GI disturbance



Statin Pharmacokinetics

Parameter	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
Isoenzyme	3A4	3A4	**None**	2C9	3A4	2C9/2C19
Lipophilic	Yes	Yes	No	Yes	Yes	No
Protein binding (%)	>95	95–98	~50	>90	96	88
Active metabolites	Yes	Yes	No	No	Yes	Yes
Elimination half-life (h)	3	2	1.8	1.2	**7–14**	**13–20**

Statin Choice

Choose medication and dose to achieve the desired LDL-C reduction intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Lowers LDL-C >=50%	*Lowers LDL-C 30-50%*	*Lowers LDL-C < 30%*
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvstatin 10-40 mg- FDA does not recommend use of simvastatin 80 mg due to increased risk of myopathy Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg* Fluvastatin 40 mg BID Pitavastatin 2-4 mg*	Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg * Pitavastatin 1 mg*

* Never tested in RCT

Bile Acid Resins

- Colestipol, cholestyramine, colesevelam
- Bind intestinal bile acid
  - Increase fecal bile excretion
  - Stimulate bile acid synthesis from cholesterol
  - Upregulate LDL receptors
- Normally 2nd-line agents when statins not sufficient or not tolerated
- May aggravate hypertriglyceridemia
  - Caution if TG > 200 mg/dL
  - Contraindicated if TG > 400 mg/dL
- Adverse effects:
  - GI distress, constipation
    - Titrate slowly, increase fluid intake, increase dietary bulk, add stool softeners
  - Hypernatremia, hyperchloremia
  - Impair fat soluble vitamin absorption
    - A, D, E, K
  - Reduce bioavailability of other medications
    - Warfarin, levothyroxine, digoxin
    - Dose 6 hrs from other medications to avoid interactions

Bile Acid Resins

- Low doses well-tolerated
- Often used in combination with other drugs
- With proper counseling & dose titration; many patients tolerate higher doses
- Tablet formulation may increase palatability; however, tablets are large
- Mix powder with liquids or food such as orange juice, oatmeal, applesauce
- Colestipol: odorless, tasteless

Nicotinic Acid/Niacin

- IR, SR, & ER formulations
- OTC & Rx (Niaspan®)
- Decreases LDL & TG
- Increases HDL
- May exacerbate gout & DM
  - Monitor closely
  - Slow dose titration
- Contraindications: active liver disease, severe gout
- Combination with statin or gemfibrozil therapy increases myopathy risk
- Adverse effects:
  - Cutaneous flushing, itching
    - ASA 325mg 30 min prior
    - Titrate dose slowly, avoid spicy foods/hot beverages
  - GI intolerance
  - Acanthosis nigricans (marker for insulin resistance)
  - Elevated LFTs, hyperuricemia, hyperglycemia
  - Niacin associated hepatitis
    - More common with SR

Fibric Acids

- Gemfibrozil, fenofibrate, clofibrate
- Reduce TG
- May result in concurrent increase in LDL
- TC remains fairly unchanged
- May increase HDL $\geq$ 10 to 15%
- 20 to 25% LDL reduction in patients with heterozygous familial hypercholesterolemia
- Efficacy depends on lipoprotein type, baseline TG
- Gemfibrozil dosed BID 30 min before meals
- Fenofibrate can be taken without regards to food
- CI in renal failure
- Combination therapy with niacin or statins increases risk of muscle toxicity

Fibric Acids…

- Adverse Effects:
  - GI complaints, rash, myalgia, headache, fatigue
  - Transient increase in transaminase & alkaline phosphatase
  - Gallstones (clofibrate)
  - Enhanced hypoglycemic effects in patients on sulfonylureas
  - May potentiate effects of oral anticoagulants
    - Monitor PT/INR closely in patients on anticoagulants

Absorption Inhibitor

- Ezetimibe
- Inhibits cholesterol absorption across the gut by 23 to 50%; hepatic LDL synthesis upregulation partially offsets impaired absorption.
- Often used in combination with statins, other drugs
- Dosed once daily without regard to meals
- ~18% LDL reduction
- Effect of ezetimibe on CV morbidity & mortality unknown

Omega 3 Fatty Acids

- Diets rich in omega 3 fatty acids from oily fish decrease TC, TG, LDL, increase HDL & decrease CV events.
- Rx fish oil: Lovaza®
  - Lowers TG 14 to 30%
  - Raises HDL ~10%
- FDA approved as dietary adjunct for very high TG levels (> 500 mg/dL)
- Thrombocytopenia, bleeding disorders: potential complication of high doses
- ≤ 3 g/day generally recognized as safe
- Until further research is done on nutraceuticals it is recommended that patients get dietary EPA & DHA.
- 2 to 4 g of EPA & DHA may be used for very high TG
- Adverse effects:
  - GI disturbance
  - Fishy aftertaste
  - Increased bleeding risk
  - Worsening glycemic control
  - Increased LDL
  - Abnormal LFTs

Hypertriglyceridemia

- Lipoprotein types I, III, IV, V associated with hypertriglyceridemia
- Exclude 1˚lipoprotein disorders & underlying diseases prior to implementing therapy
- TLC
  - Achieve desirable body weight
  - Diet low in saturated fat, cholesterol
  - Regular exercise
  - Smoking cessation
  - Alcohol restriction
- Non-HDL = total cholesterol – HDL
  - LDL + VLDL
  - 2˚ target when TG $\geq$ 200 mg/dL
  - Goal
    - 30 mg/dL higher than LDL
    - Normal VLDL: 30 mg/dL

Hypertriglyceridemia

- Borderline-high TGs + CHD risk factors
  - Family history of premature CHD
  - Concomitant LDL elevation or low HDL
  - Genetic forms of hypertriglyceridemia associated with CHD
    - Familial dysbetalipoproteinemia
    - Familial combined hyperlipidemia
  - Consider initiation of niacin
    - Caution in DM patients
- Alternatives therapies:
  - Gemfibrozil
  - Statins
    - Modest TG reduction & HDL elevation
    - Higher doses may reduce HDL, LDL, TGs
      - Related to baseline concentration, dose
  - Fish oil
  - Fibrates
    - may increase LDL
    - monitor carefully with borderline-high triglyceridemia

Hypertriglyceridemia

- Very high TGs (> 500 mg/dL) associated with pancreatitis
- TG > 500 mg/dL: genetic form of hypertriglyceridemia often coexists with other causes (e.g. DM)
  - dietary fat restriction (10% to 20% of calories)
  - weight loss
  - alcohol restriction
  - treat coexisting disorders
- Medications for TG > 500 mg/dL
  - Gemfibrozil: preferred in diabetics
  - Niacin
  - Higher-potency statins: atorvastatin, rosuvastatin, simvastatin
  - Fenofibrate may be preferred in combination with statins
    - Does not impair glucuronidation
    - Minimizes potential drug interactions
- Successful treatment: TG < 500 mg/dL

Low HDL-C

- Low HDL: strong independent CHD risk predictor
- ATP III: low HDL-C < 40 mg/dL
- No specific goal for HDL-C raising
- Causes of low HDL
  - Insulin resistance
  - Physical inactivity
  - Type 2 diabetes mellitus
  - Cigarette smoking
  - Very high carbohydrate intake
  - Certain drugs
- LDL remains ATP III 1˚ target
- ATP III recommendations:
  - Weight reduction
  - Increased physical activity
  - Smoking cessation
  - Drug therapy
    - Fibric acid derivatives
    - Niacin
      - potential for greatest HDL increase
      - Effect more pronounced with regular or IR forms than SR

Diabetic Dyslipidemia

- Characterized by hypertriglyceridemia, low HDL, & minimally elevated LDL
- Small, dense LDL in DM patients is more atherogenic than larger, more buoyant LDL
- 1˚target: LDL
- Goal of treatment: LDL-C < 100 mg/dL
- LDL > 130 mg/dL: TLC + drug therapy often required
- Statins often considered initial drugs of choice
- Collaborative Atorvastatin Diabetes Study (CARDS)
- LDL lowering for 1˚ CHD prevention in type 2 DM
- Randomized, double-blinded placebo controlled
- Atorvastatin 10 mg/day versus placebo (n=2,838) diabetes to reduce first CHD events
- Baseline LDL: 118 mg/dL; LDL ↓ 46 mg/dL with atorvastatin

Diabetic Dyslipidemia

- CARDS trial: 37% reduction in composite 1˚end point
- 1˚ endpoint: acute CHD death, nonfatal MI, hospitalized unstable angina, resuscitated cardiac arrest, coronary revascularization, or stroke
- Suggests diabetics should have target LDL much lower than 100 mg/dL

Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of CV disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696.

Elderly Patients

- More susceptible to adverse effects of lipid-lowering drug therapy
- Start with lower doses, titrate slowly to minimize adverse effects
- Risks or benefits from cholesterol reduction not well defined

Women

- Cholesterol: important CHD determinant
  - Relationship not as strong as for women as men
- HDL may be more important predictor of disease in women
- No apparent difference between men & women in LDL/HDL genetic regulation

Hyperlipidemia in Pregnancy

- TC & TG levels increase throughout pregnancy
  - Average cholesterol increase: 30 to 40 mg/dL around weeks 36 to 39.
  - TGs may increase as much as 150 mg/dL
- Drug therapy typically not initiated/continued during pregnancy
- TLC is the mainstay but BARs & absorption inhibitors may be considered in high risk patients
  - ezetimibe: category C
- Statins: category X

Children

- Drug therapy not recommended age < 8 yrs
- Different guidelines, goals
- Bile acid sequestrants 1st-line in the past
  - GI adverse effects limit use
- New evidence shows statins are safe & effective in children
  - Greater lipid lowering than BAR
  - Severe forms may require more aggressive treatment
    - e.g., Familial hypercholesterolemia

Concurrent Disease States

- Nephrotic syndrome, end-stage renal disease, HTN compound dyslipidemia risks
  - May be difficult-to-treat
- Nephrotic syndrome lipoprotein metabolism abnormalities
  - Elevated TC, LDL-C, lipoprotein(a), VLDL, TGs
- Statins reduce TC & LDL-C in nephrotic syndrome
  - Levels do not usually return to normal
  - May slow declining renal function
- Renal insufficiency without proteinuria: hypertriglyceridemia, slightly elevated TC & LDL-C, low HDL
- Polyunsaturated fatty acids may slow pregression of renal disease & CV complications
- Bile acid sequestrants do not correct lipid abnormalities seen in renal insufficiency

Concurrent Disease States

- Lovastatin or its active metabolite may accumulate in renal insufficiency, use lower doses to avoid adverse effects
- Treat CKD patients to LDL goal < 100 mg/dL
  - lowering LDL to < 70 in high risk patients not supported by clinical trials
- Hypertensive patients: greater-than-expected prevalence of hypercholesterolemia
- Patients with hypercholesterolemia have a higher than expected prevalence of HTN
  - Caused by metabolic syndrome
- HTN management
  - Avoid drugs that elevate cholesterol
    - diuretics
    - α-blockers
  - Niacin may magnify vasodilator hypotensive effects

Dyslipidemia in CKD Patients

Dyslipidemia	Goal	Initial Therapy	Modification in Therapy	Alternative
TG 500 mg/dL	TG < 500 mg/dL	TLC	TLC + fibrate or niacin	Fibrate or niacin
LDL 100–129 mg/dL	LDL < 100 mg/dL	TLC	TLC + low-dose statin	Bile acid sequestrant or niacin
LDL 130 mg/dL	LDL < 100 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Bile acid sequestrant or niacin
TG 200 mg/dL and non-HDL 130 mg/dL	Non-HDL < 130 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Fibrate or niacin

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Non-HDL, total cholesterol minus HDL cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes.

Concurrent Disease States

- Use gemfibrozil with caution
  - pharmacokinetics unchanged
    - lowers TGs
    - increases HDL
- Combination statins & fibric acid derivatives increases risk of severe myopathy
  - monitor for myositis
- Niacin may be useful in nondiabetic patients with renal insufficiency

Monitoring

Statins	Baseline FLP, LFTs, CK Repeat LFTs at 6 weeks, 3 months, periodically
Bile Acid Resins	Baseline FLP Repeat FLP at 6 weeks, periodically
Nicotinic Acid	Baseline FLP, glucose, LFTs, uric acid Repeat all tests 4-6 weeks after dose change
Fibric Acid	Baseline FLP Repeat FLP at 12 months, periodically
Cholesterol Inhibitors	Baseline FLP Repeat FLP at 6 weeks, periodically

Hypertension

Source: Schwinghammer TL: *Pharmacotherapy Casebook: A Patient-Focused Approach,* 7th Edition: http://www.accesspharmacy.com

Objectives

❖ **Upon Completion of the session, the students Will be able to:**

- Describe arterial blood pressure (BP), the regulation of BP, and the pathophysiology of hypertension.
- Identify hypertension-related target-organ damage
- Classify blood pressure levels and treatment goals.
- Recognize the underlying causes and contributing factors in the development of hypertension.
- Recommend appropriate lifestyle modifications and pharmacotherapy for patients with hypertension.
- Identify populations requiring special consideration when designing a treatment plan.
- Construct an appropriate monitoring plan to assess hypertension treatment.

Overview

- Definition, classification of hypertension (HTN)
- Goals of therapy
- Compelling indications
- Lifestyle modifications
- Hypertension in pregnancy
- Treatment
- Orthostatic hypotension
- Hypertensive crisis
- Monitoring antihypertensive drug therapy

Hypertension

- Persistent elevation of arterial blood pressure (BP) ≥140/≥90 mmHg.
- The JNC8 diagnosis of BP is based on the average of two or more properly measured BP readings from two or more clinical encounters.
- Hypertension is a major risk factor for many forms of heart disease and stroke
- Can accelerate damage to the arterioles, lead to formation of plaques on the artery walls leading to arteriosclerosis.
- Secondary to chronic hypertension, the brain, the eyes, the heart, and the kidneys can be affected and damaged
- Target-Organ Damage;
  - **Brain**: stroke, transient ischemic attack, dementia.
  - **Eyes**: retinopathy
  - **Heart**: left ventricular hypertrophy, angina.
  - **Kidney**: chronic kidney disease.
  - **Peripheral Vasculature**: peripheral arterial disease.

Epidemiology

- Approximately one in three adult (age 20 years or older) Americans have elevated BP.
- The overall incidence is similar between men and women, but varies depending on age.
  - The percentage of men with high BP is higher than for women before the age of 45 and is similar to that of women between the ages 45 and 64.
  - However, after the age of 64, a much higher percentage of women have high BP than men.
- BP values increase with age, and HTN is very common in the elderly.
  - The lifetime risk of developing HTN among those 55 years of age and older who are normotensive is 90%.
- Prevalence differs by ethnic group(African Americans Vs Asia Americans).

Etiology

1. Essential or primary HTN

- >90% of individuals with high BP have essential HTN.
- Results from unknown pathophysiological etiology.
- Numerous mechanisms have been identified that may contribute to the pathogenesis.
- Genetic factors may play an important role in the development.
- Cannot be cured, but it can be controlled.

2. Secondary Hypertension

- <10% of patients have secondary hypertension
- Where either a comorbid disease or drug (or other product) is responsible for elevating BP.
- Severe CKD or renovascular disease is the most common secondary cause.
- Certain drugs (or other products), either directly or indirectly, can cause or exacerbate HTN.
- The HTN in these pts can be mitigated or potentially be cured.

Causes of 2° Hypertension

- **Diseases**
  - Chronic kidney disease
  - Cushing's syndrome
  - Coarctation of the aorta
  - Obstructive sleep apnea
  - Parathyroid disease
  - Pheochromocytoma
  - Primary aldosteronism
  - Renovascular disease
  - Thyroid disease
- **Prescription drugs**:
  - Prednisone, fludrocortisone, triamcinolone
  - Amphetamines/Anorexiants: phendimetrazine, phentermine, sibutramine
  - Antivascular endothelin growth factor agents
  - Estrogens: usually oral contraceptives
  - Calcineurin inhibitors: cyclosporine, tacrolimus
  - decongestants: phenylpropanolamine & analogs
  - Erythropoiesis stimulating agents: erythropoietin, darbepoietin

Causes of 2° Hypertension

- Prescription drugs:
  - NSAIDS, COX-2 Inhibitors
  - Venlafaxine
  - Bupropion
  - Bromocriptine
  - Buspirone
  - Carbamazepine
  - Clozapine
  - Ketamine
  - Metoclopramide
- Situations:
  - β-blocker or centrally acting α-agonists
    - when abruptly discontinued
  - β-blocker without α-blocker first when treating pheochromocytoma.
- Food substances:
  - Sodium
  - Ethanol
  - Licorice

Causes of 2° Hypertension

- Street drugs, other natural products:
  - Cocaine
  - Cocaine Withdrawal
  - Ephedra Alkaloids
  - "Herbal Ecstasy"
  - Phenylpropanolamine Analogs
  - Nicotine Withdrawal
  - Anabolic steroids
  - Narcotic Withdrawal
  - Methylphenidate
  - Phencyclidine
  - Ketamine
  - Ergot-containing Herbal Products
  - St. John's Wort

Pathophysiology

- Multiple factors that control BP are potential contributing components in the development of essential HTN.
- These include malfunctions in;
  - Either humoral [i.e., the renin-angiotensin-aldosterone system (RAAS)] or vasodepressor mechanisms,
  - Abnormal neuronal mechanisms
  - Defects in peripheral autoregulation, and
  - Disturbances in sodium, calcium, and natriuretic hormone.

Arterial BP

- The pressure in the arterial wall measured in mm hg.
- The two typical arterial bp values are sbp & dbp.
- Sbp represents the peak value, which is achieved during cardiac contraction.
- Dbp is achieved after contraction when the cardiac chambers are filling, and represents the nadir value.
- The difference between sbp and dbp is called the pulse pressure and is a measure of arterial wall tension.
- Mean arterial pressure (map) is the average pressure throughout the cardiac cycle of contraction.
- It is sometimes used clinically to represent overall arterial BP, especially in hypertensive emergency.
- During a cardiac cycle, two-thirds of the time is spent in diastole and one-third in systole.
  - **Hence; MAP = 1/3SBP + 2/3DBP**
- Arterial BP is mathematically defined as the product of cardiac output(CO) and total peripheral resistance(TPR):
  - **BP = CO x TPR**
- CO is a function of stroke volume, heart rate, and venous capacitance

Main sites and mechanisms of BP control

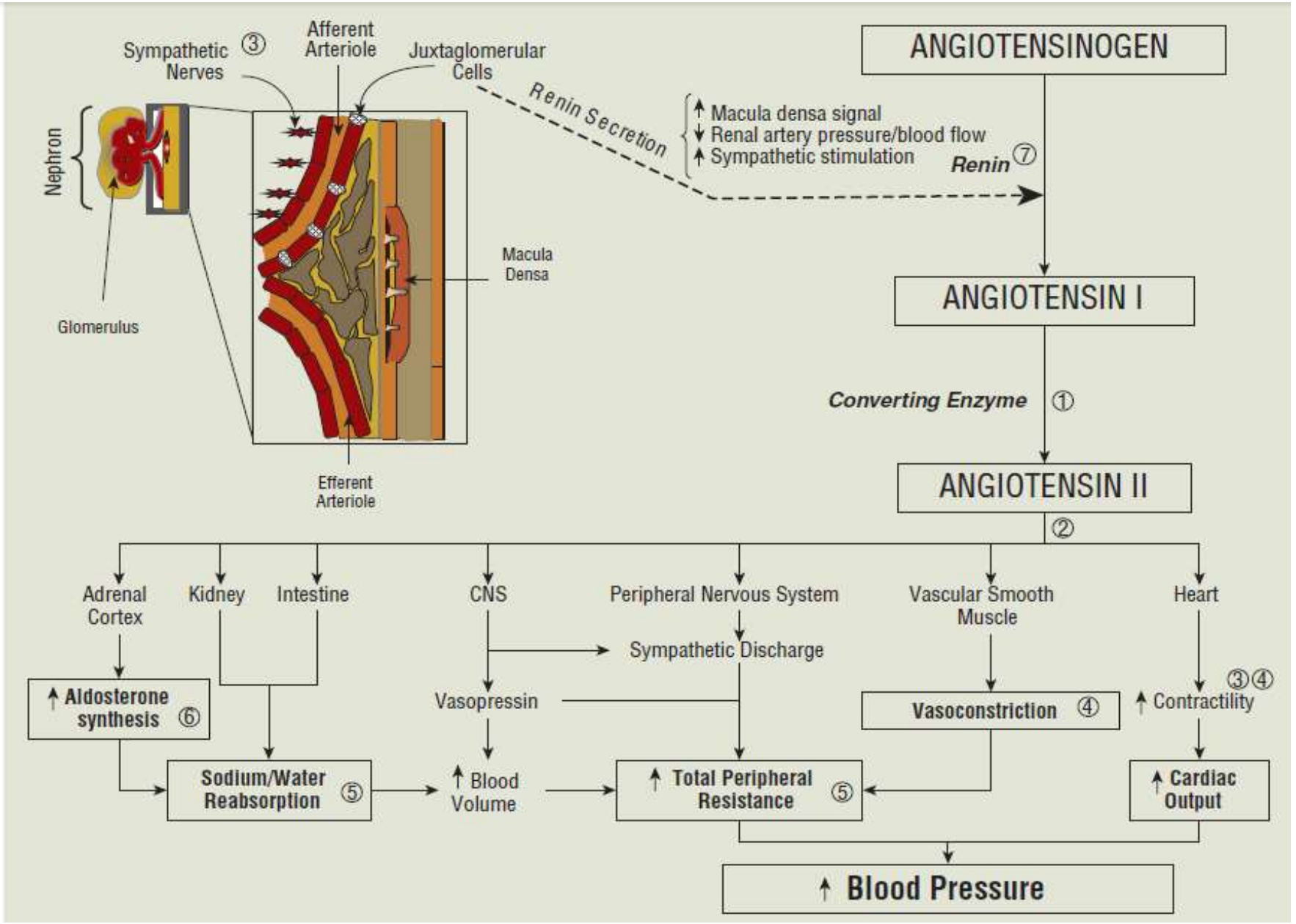
1. **Baroreceptor reflex:**
   - Mediated by autonomic nerves
2. **Humoral mechanism:**
   - The Renin-Angiotensin-Aldosterone system (RAAS)
   - Natriuretic hormone, and
   - Hyperinsulinemia

Baroreceptor Reflex

- For rapid adjustment of BP
  - Sensory input: receptors on carotid sinus and aortic arc
  - Stimulus: stretch
- If BP is increased
  - Carotid receptors are stimulated by stretch of blood vessels
  - Results in the inhibition of sympathetic discharge
- If BP is decreased
  - Stretch of blood vessels is reduced $\Rightarrow \downarrow$sed baroreceptor activity
  - $\Rightarrow$ Disinhibition of sympathetic discharge

Humoral Control

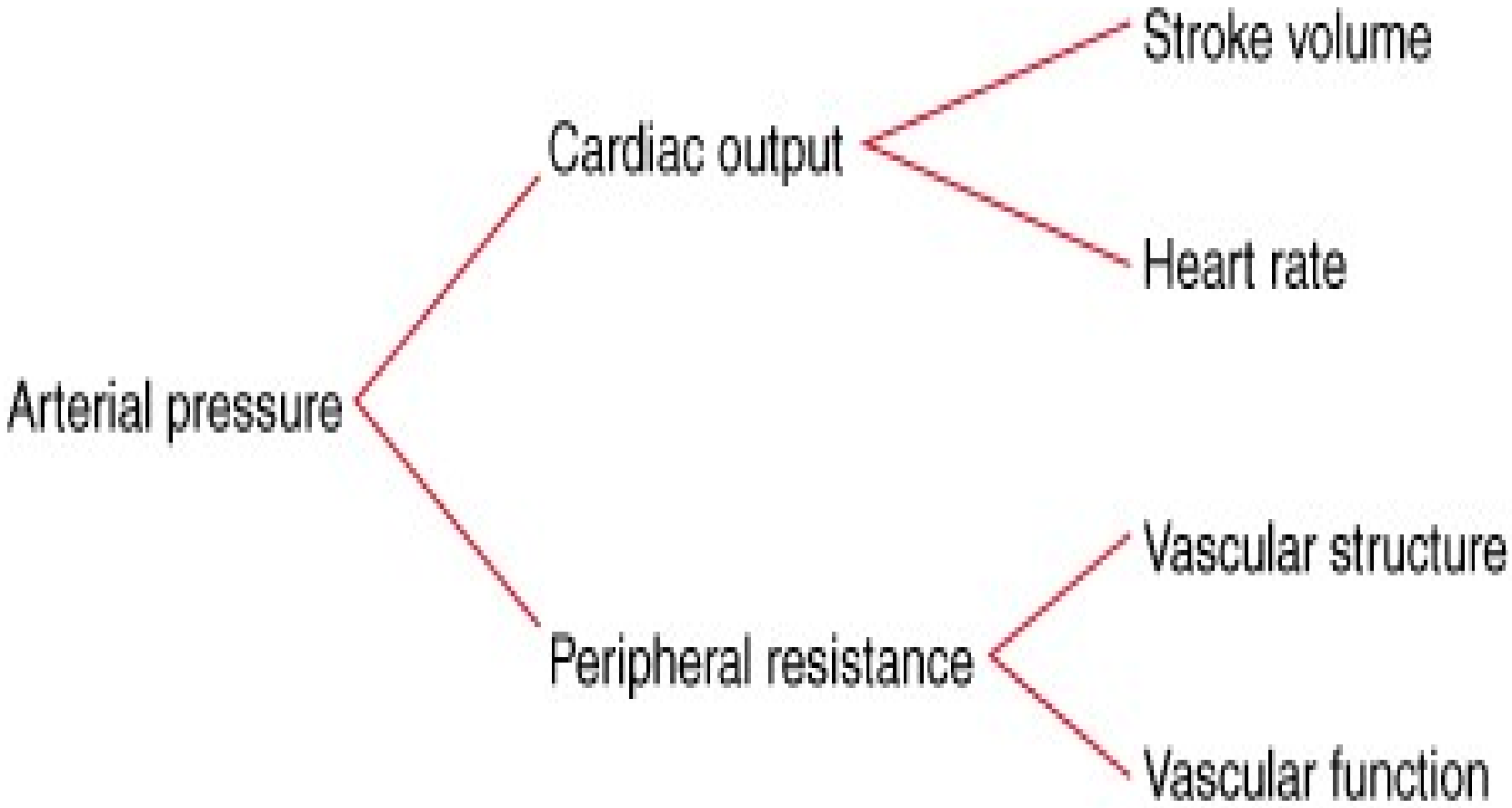
- For long term control of BP
- If mean arterial BP is reduced,
  - Renal perfusion pressure is reduced
  - Increased reabsorption of salt & water
  - Increased secretion of renin and the resulting increase in Angiotensin II, which in turn causes:
    - Direct arteriolar vasoconstriction
    - Increased secretion of aldosterone


Sympathetic Nerves ③
Afferent Arteriole
Juxtaglomerular Cells
Nephron
Glomerulus
Macula Densa
Efferent Arteriole
Renin Secretion
↑ Macula densa signal
↓ Renal artery pressure/blood flow
↑ Sympathetic stimulation
Renin ⑦
ANGIOTENSINOGEN
ANGIOTENSIN I
Converting Enzyme ①
ANGIOTENSIN II
②
Adrenal Cortex
Kidney
Intestine
CNS
Peripheral Nervous System
Vascular Smooth Muscle
Heart
↑ Aldosterone synthesis ⑥
Sympathetic Discharge
Vasopressin
Vasoconstriction ④
↑ Contractility
③④
Sodium/Water Reabsorption ⑤
↑ Blood Volume
↑ Total Peripheral Resistance ⑤
↑ Cardiac Output
↑ Blood Pressure

Mechanisms of Pathogenesis

- CO is the major determinant of SBP, whereas TPR largely determines DBP
- Elevated BP can result from increased cardiac output and/or increased total peripheral resistance
- Increased cardiac output (CO):
  - Increased preload:
    - Increased fluid volume
    - Excess sodium intake
    - Renal sodium retention
  - Venous constriction:
    - Excess RAAS stimulation
    - Sympathetic nervous system overactivity

Arterial Pressure Determinants



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Mechanisms of Pathogenesis

- Increased peripheral resistance (PR):
  - Functional vascular constriction:
    - Excess RAAS stimulation
    - Sympathetic nervous system overactivity
    - Genetic alterations of cell membranes
    - Endothelial-derived factors
  - Structural vascular hypertrophy:
    - Excess RAAS stimulation
    - Sympathetic nervous system overactivity
    - Genetic alterations of cell membranes
    - Endothelial-derived factors
    - Hyperinsulinemia due to obesity, metabolic syndrome

Classification

- Based on the average of 2 or more measurement $\rightarrow$ 4 categories

Classification	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)
Normal	Less than 120	and	Less than 80
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	$\geq$ 160	or	$\geq$ 100

If systolic and diastolic BP values yield different classifications, the highest category is used for the purpose of determining a classification.

Classification

- Isolated systolic hypertension (ISH)
  - When SBP > 140 and DBP < 90
- White coat hypertension: Elevated BP in clinic followed by normal BP reading at home
- Masked hypertension: where a decrease in BP occurs in the clinical setting
- Hypertensive crises: very elevated, typically greater than 180/120 mm Hg.
  - Hypertensive emergency or hypertensive urgency.
- Resistant HTN
  - Patients failing to achieve goal blood pressure despite maximum doses of three antihypertensives including a diuretic

Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

Causes of Resistant Hypertension

Improper blood pressure measurement

Volume overload
- Excess sodium intake
- Volume retention from kidney disease
- Inadequate diuretic therapy

Ineffective cardiac pump function
- Diastolic dysfunction

Drug-induced
- Non-steroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
- Cocaine, amphetamines, and other illicit drugs
- Sympathomimetics (decongestants, anorectics, and stimulants)
- Oral contraceptive hormones
- Adrenal steroid hormones
- Cyclosporine and tacrolimus
- Erythropoietin
- Licorice (including some chewing tobacco)
- Select over-the-counter dietary supplements and non-traditional medicines (e.g., ephedra, ma huang, and bitter orange)

Therapeutic circumstances
- Failure to receive or take antihypertensive medications
- Inadequate doses (sub-therapeutic)
- Improper antihypertensive selection or combination
- Drug-drug or drug-food interactions

Associated conditions
- Obesity
- Excess alcohol intake

Children And Adolescent

•Normal BP – Both systolic and diastolic BP <90th percentile.

•Prehypertension – Systolic and/or diastolic BP ≥90th percentile but <95th percentile **or** if BP exceeds 120/80 mmHg even if <90th percentile. Prehypertension is predictive of hypertension. This was illustrated in one study based upon the National Childhood Blood Pressure database that demonstrated 14 percent of male and 12 percent female adolescents were hypertensive two years later.

•Hypertension – HTN is defined as either systolic and/or diastolic BP ≥95th percentile measured upon three or more occasions.

•The degree of HTN is further delineated by the two following stages:

•**Stage 1 hypertension** – Systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile.

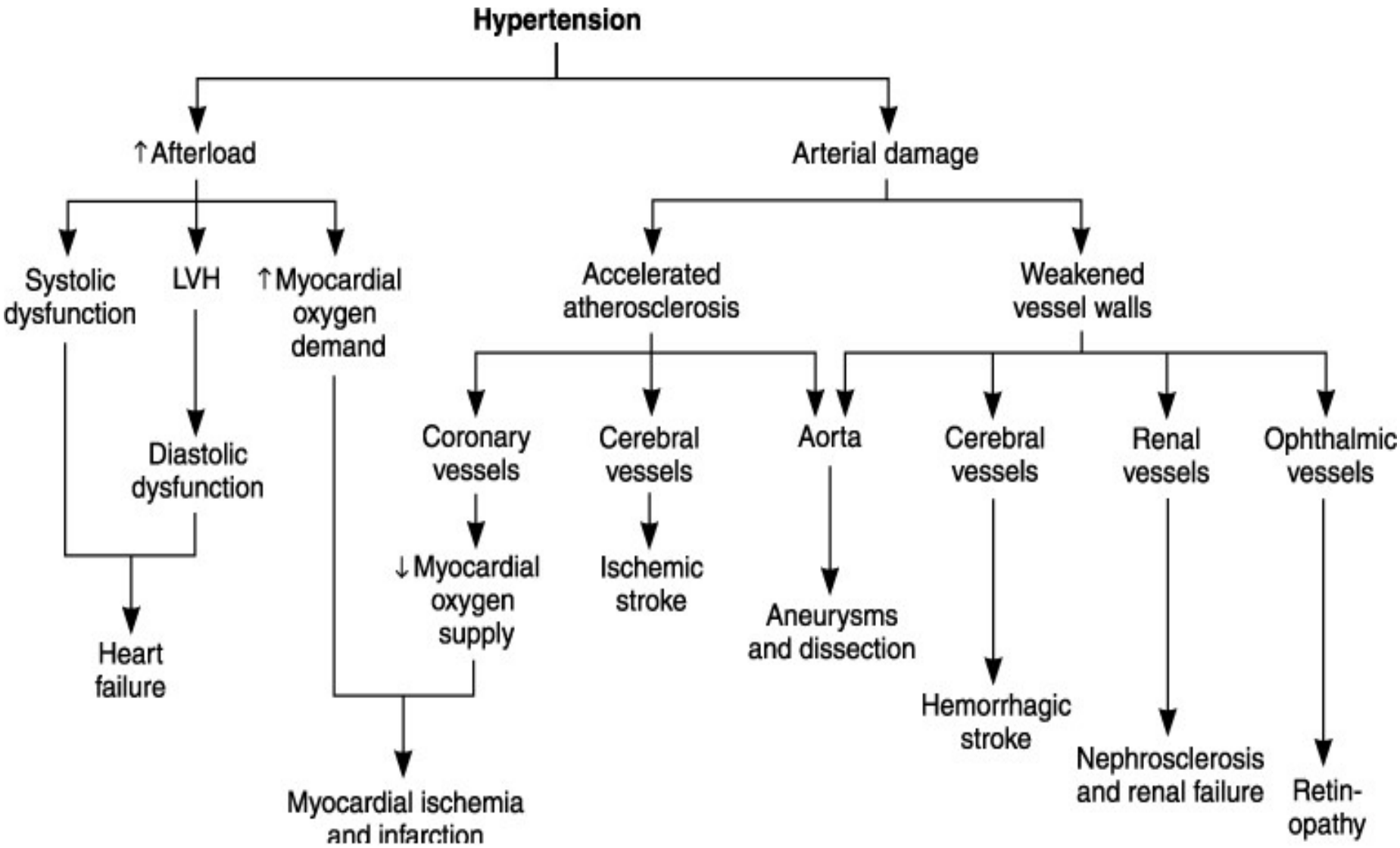
•**Stage 2 hypertension** – Systolic and/or diastolic BP ≥99th percentile plus 5 mmHg.

Clinical Presentation

- **General:**
  - The patient may appear healthy or may have the presence of additional CV risk factors:
    - Age (greater than or equal to 55 for men, greater than or equal to 65 for women)
    - Diabetes mellitus
    - Dyslipidemia
    - Microalbuminuria
    - Family history of premature CV disease
    - Obesity (body mass index greater than or equal to 30 kg/m2)
    - Physical inactivity
    - Tobacco use

Clinical Presentation

- **Symptoms:**
  - Usually none related to elevated BP. (silent killer)
- **Signs:**
  - Previous BP values in either the preHTN or the HTN category
- **Laboratory Tests:**
  - BUN/serum creatinine, fasting lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium), spot urine albumin-to-creatinine ratio.
- **Other Diagnostic Tests:**
  - 12-lead ECG, estimated glomerular filtration rate [using modification of diet in renal disease (MDRD) equation].
- **Hypertension-Related Target-Organ Damage:**
  - Brain (stroke, transient ischemic attack, dementia)
  - Eyes (retinopathy)
  - Heart (left ventricular hypertrophy, angina, prior MI, prior coronary revascularization, heart failure)
  - Kidney (chronic kidney disease)
  - Peripheral vasculature (peripheral arterial disease)



Source: McPhee SJ, Ganong WF: *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th Edition: http://www.accessmedicine.com

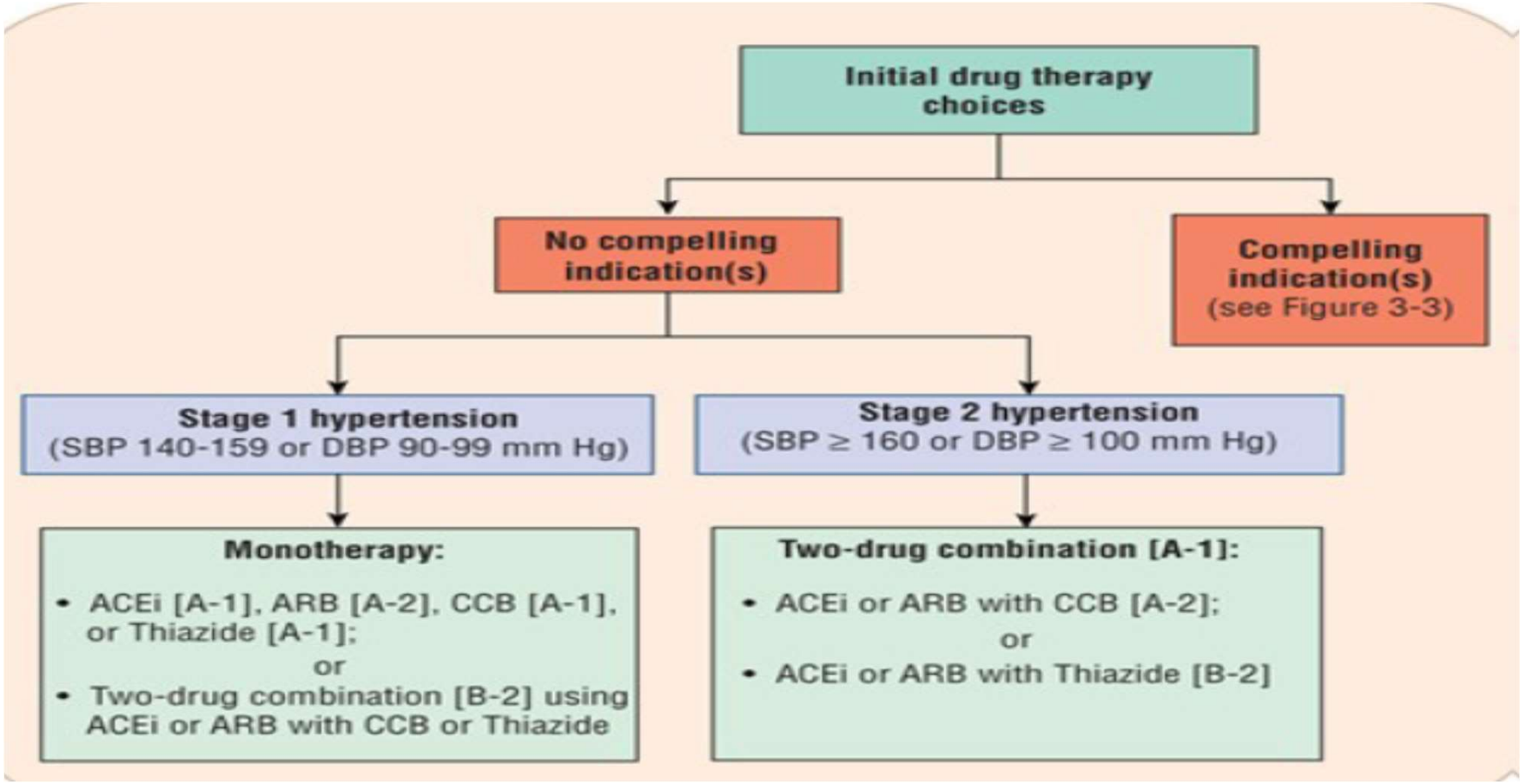
Treatment

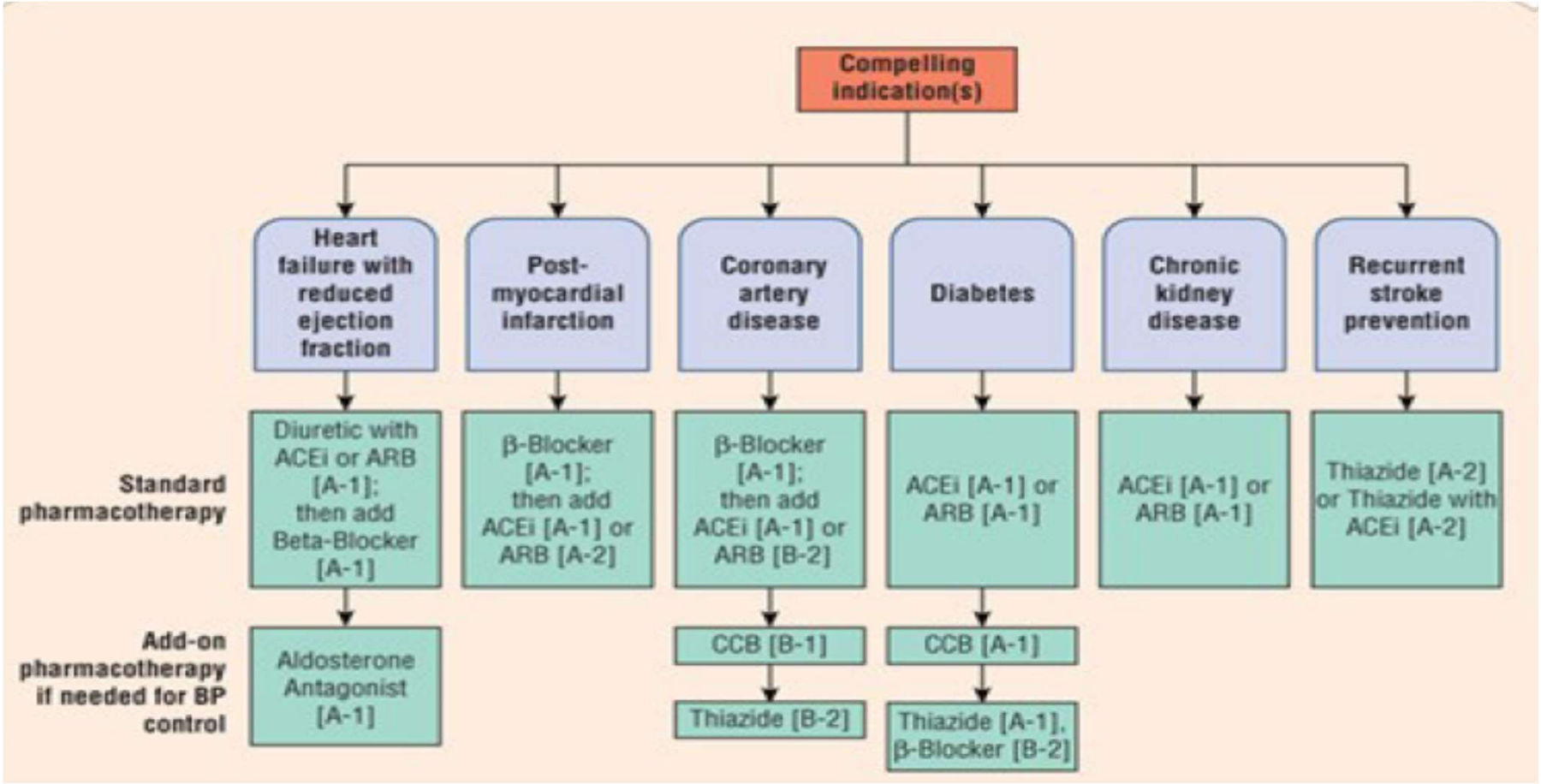
- Desired Outcomes
  - Overall Goal of Treatment
    - Reduce morbidity & mortality
    - Select drug therapy based on evidence demonstrating risk reduction
  - Surrogate goal of therapy
    - Achieve a desired target value

Patient Population	Target Blood Pressure
For Most patients including diabetes and /or CKD and the elderly	< 140/90 mmHg
Frail elderly at high risk for serious adverse effects	< 150/90 mmHg
CKD with persistent urine albumin excretion	<130/80 mmHg
Younger DM patients (optional)	<130/80 mmHg
Framingham risk score of 15% or greater and age . 50 years	SBP <120 mmHg

General Approach to Treatment

- Lifestyle modifications and drug therapy concurrently.
- Lifestyle modification alone for prehypertension.
- The choice of initial drug therapy depends on
  1. **Degree of BP elevation** and
     - Stage 1 (one 1st line drug)
     - Stage 2 (combination of two 1st line drugs)
  2. **Presence of compelling indications.**
- Six compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with HTN.
- The listed compelling indication
  - Heart Failure
  - Post Myocardial Infarction
  - High Coronary Disease Risk
  - Diabetes Mellitus
  - Chronic Kidney Disease
  - Recurrent Stroke Prevention


Initial drug therapy choices
No compelling indication(s)
Compelling indication(s) (see Figure 3-3)
Stage 1 hypertension (SBP 140-159 or DBP 90-99 mm Hg)
Stage 2 hypertension (SBP ≥ 160 or DBP ≥ 100 mm Hg)
Monotherapy:
• ACEi [A-1], ARB [A-2], CCB [A-1], or Thiazide [A-1];
or
• Two-drug combination [B-2] using ACEi or ARB with CCB or Thiazide
Two-drug combination [A-1]:
• ACEi or ARB with CCB [A-2];
or
• ACEi or ARB with Thiazide [B-2]


Compelling indication(s)
Heart failure with reduced ejection fraction
Post-myocardial infarction
Coronary artery disease
Diabetes
Chronic kidney disease
Recurrent stroke prevention
Standard pharmacotherapy
Diuretic with ACEi or ARB [A-1]; then add Beta-Blocker [A-1]
β-Blocker [A-1]; then add ACEi [A-1] or ARB [A-2]
β-Blocker [A-1]; then add ACEi [A-1] or ARB [B-2]
ACEi [A-1] or ARB [A-1]
ACEi [A-1] or ARB [A-1]
Thiazide [A-2] or Thiazide with ACEi [A-2]
Add-on pharmacotherapy if needed for BP control
Aldosterone Antagonist [A-1]
CCB [B-1]
CCB [A-1]
Thiazide [B-2]
Thiazide [A-1], β-Blocker [B-2]

Nonpharmacologic Therapy: Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Recommendation	Approximate SBP Reduction (mm Hg)
Weight loss	Maintain normal body weight (body mass index, 18.5–24.9 kg/m^2)	5–20 per 10-kg weight loss
DASH-type dietary patterns	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to 65 mmol/day (1.5 g/day sodium, or 3.8 g/day sodium chloride) Encourage Potassium intake (ideally 4.7 g/day)	2–8
Physical activity	Regular aerobic physical activity (at least 30 minutes/day, most days of the week)	4–9
Moderation of alcohol intake	Limit consumption to ≤2 drink equivalents per day in men and ≤1 drink equivalent per day in women and lighter weight persons [b]	2–4

Smoking is a major, independent, modifiable risk factor for CV disease.

DASH, Dietary Approaches to Stop Hypertension.

Pharmacotherapy

- Reduces the risk of hypertension-associated complications (e.g., CV morbidity and mortality)
- **Initial Drugs of Choice for Hypertension**
  - ACE inhibitor (ACEI)
  - Angiotensin receptor blocker (ARB)
  - Thiazide diuretic
  - Calcium channel blocker (CCB)
- Produces a substantial reduction:
  - ✓ ≈40% risk of stroke
  - ✓ 50% risk of heart failure & incidence of renal failure
  - ✓ 25% risk of coronary artery disease in the elderly
- Treatment regimens that are based on
  - ✓ Diuretics, CCBs, ACEIs/ARBs have generally shown equal efficacy for reducing events
- In contrast, β-adrenoceptor antagonists are less effective at preventing the complications of HTN and are no longer recommended as first-line therapy

Drug Regimens In Hypertension

Stepped approach

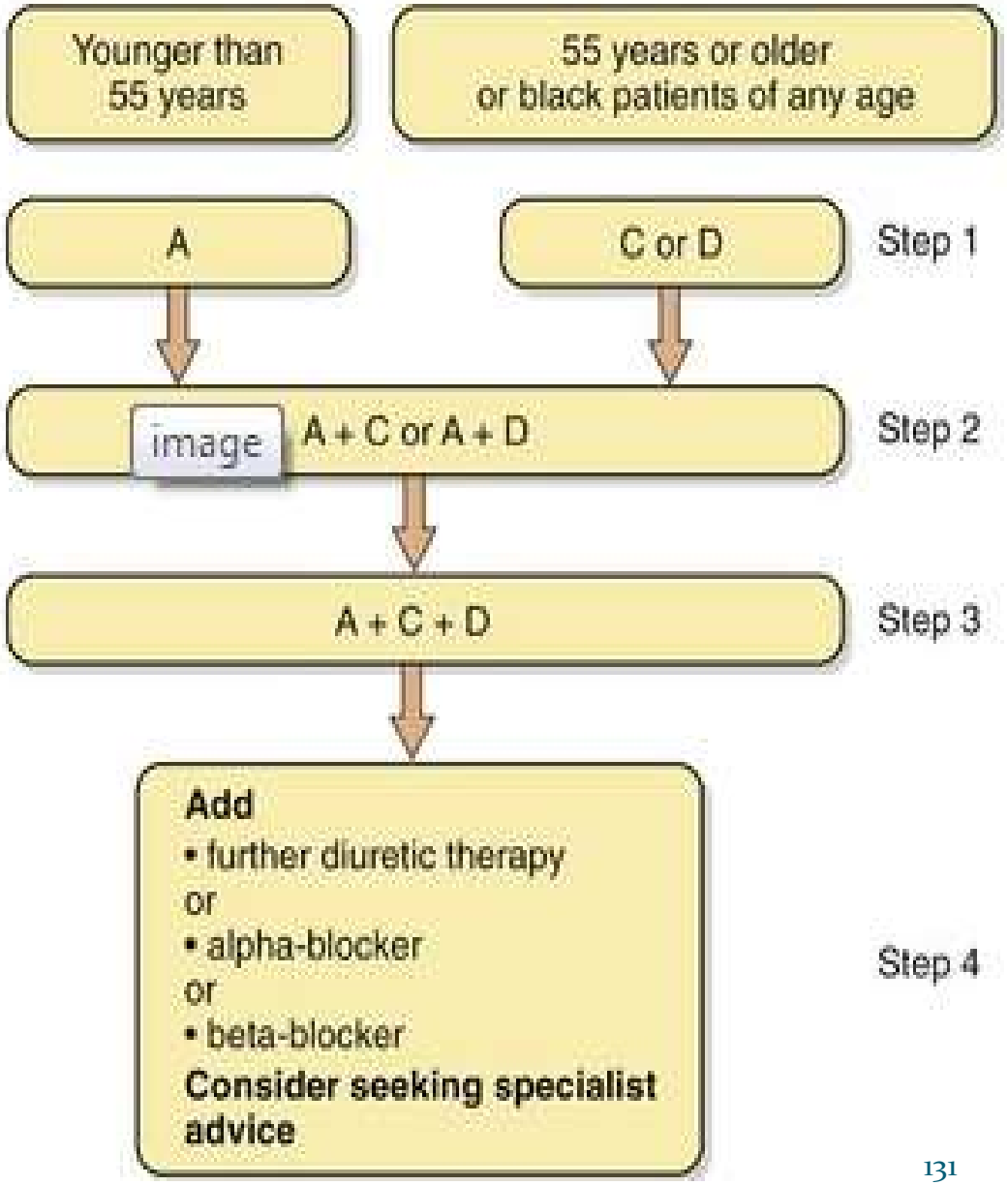
- Treatment of HTN should follow a 'stepped care' approach
- A stepped-care approach "involves the sequential addition of medications until BP i

  - Substitution therapy, if the first chosen drug either
    - Does not lower BP
    - Associated with serious or bothersome adverse effects
    - Best applied to stage 1 HTN because a single drug may often be sufficient for BP control

Choosing drugs for patients newly diagnosed with hypertension

Abbreviations:
A = ACE inhibitor
(consider angiotensin II receptor antagonist if ACE intolerant)
C = calcium channel blocker
D = thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients



Step Down Therapy

- Primary prevention patients with a goal BP *<140/90 mmHg who have very well controlled* BP for at least 1 year might be eligible for a trial of step-down therapy.

❖**This option should not be considered for patients who have**

  - a Framingham risk score≥10%,
  - Compelling indications, or
  - Hypertension-associated complications.

- Consists of attempting to gradually decrease the dosage, number of antihypertensive drugs, or both without compromising BP control.

Individual Antihypertensive Agents

Diuretics

- **Thiazide Diuretics**
  - Chlorothiazide (12.5-25 mg qd)
  - Hydrochlorothiazide (12.5-50mg qd)
  - Indapamide (1.25 -2.5 mg qd)
  - Metolazone (used in renal pts) (2.5-10mg qd)
- **Loop Diuretics**
  - Bumetanide (0.5-4mg/d BID)
  - Ethacrynic acid (used in sulfur allergic pts)
  - Furosemide (20-80mg/d bid)
  - Torsemide (5-10mg/d qd)
- **Potassium sparing diuretics**
  - Amiloride(5-10mg/d qd)
  - Triametrene (50-100mg/d qd or bid)
  - Sprinolactone
  - Eplerenone

Diuretics

- Dose in the morning and late after noon
- Thiazide, are first-line agents for HTN
- Potassium-sparing diuretics are weak antihypertensive agents but provide an additive effect when used in combination with a thiazide or loop diuretic.
- Aldosterone antagonists (spironolactone and eplerenone) may be technically considered potassium-sparing agents, but are more potent antihypertensives.
- They are viewed by the JNC7 as an independent class because of evidence supporting compelling indications.

❖ Hypotensive mechanisms of diuretics

- Initial diuresis
  - Reductions in plasma and stroke volume
  - Decreases cardiac output and BP.
    - ✓ Compensatory increase in PVR
- With chronic diuretic therapy
  - ECF and plasma volume return to near pretreatment values.
  - PVR decreases to values that are lower than the pretreatment baseline.
    - ✓ Responsible for chronic antihypertensive effects.

Adverse effects of thiazide diuretics

- Hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction
  - ✓ Identified at high dose (e.g.,HCTZ 100 mg/day)
- Current guidelines limiting the dose of HCTZ 12.5 to 50 mg/day, which markedly reduces the risk for most metabolic side effects.

Loop diuretics may cause the same side effects

- ✓ Effect on serum lipids and glucose is not as significant, and hypocalcemia may occur.
- ✓ Ototoxicity
- Less effective in CKD with GFR < 30 ml/minute – Furosemide is preferable
- **Potassium-sparing diuretics** used with great caution in CKD, ACEIs therapy , Potassium supplements
- **Parameters to monitor**
  - BP, Weight, Serum electrolytes and uric acid
  - BUN and creatinine
  - Cholesterol levels(Thiazides)
  - Hearing (in high doses)(Loop diuretics)

ACE Inhibitors

- Stops conversion of angiotensin I to angiotensin II
- ↓ Rate of deactivation of bradykinin (which is a potent vasodilator)
  - ✓ Decrease TPR
- **ACEIs are believed to provide unique CV benefits by:**
  - ✓ Improving endothelial function
  - ✓ Promoting LVH regression
  - ✓ Improving insulin sensitivity
  - ✓ Neuroprotection in diabetes and CKD with proteinuria
- Ethnic differences exist in the response to these classes of medications.
- Relatively less effective as monotherapy in **African American patients.**
- **The addition of diuretic therapy** has been shown to sensitize African American patients to these agents to obtain similar responses as in non-African American patients
- If a compelling indication, such as left ventricular dysfunction, diabetes, or chronic kidney disease is present, an ACEI is a drug of choice.

ACEI in Hypertension

Drug	Usual Starting Dose[a] (mg/day)	Usual Dosage Range (mg/day)	Dosing Frequency
Benazepril (Lotensin)	10	20–40	Daily to BID
Captopril (Capoten)	25	50–100	BID to TID
Enalapril (Vasotec)	5	10–40	Daily to BID
Fosinopril (Monopril)	10	20–40	Daily
Lisinopril (Prinivil, Zestril)	10	20–40	Daily
Moexipril (Univasc)	7.5	7.5–30	Daily to BID
Perindopril (Aceon)	4	4–16	Daily
Quinapril (Accupril)	10	20–80	Daily to BID
Ramipril (Altace)	2.5	2.5–20	Daily to BID
Trandolapril (Mavik)	1	2–4	Daily

[a]Starting dose may be decreased 50% if patient is volume depleted, in acute heart failure exacerbation, or are very elderly (≥75 yrs).

ACEIs…

When produce effect?

- Following the initiation of therapy, it may take several weeks before the full antihypertensive effects of these drugs are observed.
  - Evaluating BP response 2 to 4 weeks after starting or changing the dose of an ACEI is appropriate
- **Unwanted effects**

1. Persistent dry cough

- ✓ Due accumulation of bradykinin in the lung
- ✓ Can develop after many months of treatment- *inform the patient*
- ✓ Not dose-related
- ✓ Occurs in 10–30% of people who take ACE inhibitors.
- ✓ More common in women and African Americans

2. Postural hypotension

- ✓ Very elderly
- ✓ Volume depleted, or
- ✓ have a heart failure exacerbation.

ACEIs…

❖ **Solution in this population**

- ✓ Starting at half the standard dose of the ACEI,
- ✓ Decreasing the dose of the diuretic, or
- ✓ Stopping the diuretic before initiating the ACEI

3. **Renal impairment**

- ✓ Especially in those with severe bilateral renal artery stenosis who rely on angiotensin-mediated efferent glomerular arterial vasoconstriction to maintain glomerular perfusion pressure.
- ✓ Monitoring of serum potassium and creatinine values within 4 weeks of starting or increasing the dose of an ACEi

4. Disturbance of taste (which may be permanent),

- ✓ Nausea, vomiting, dyspepsia or bowel disturbance.

5. Rashes.

6. Neutropenia

7. Angioedema –more likely in African Americans and smokers.

Symptoms include

- ✓ lip and tongue swelling and possibly difficulty breathing.
- ✓ Drug discontinuation is needed for ACE inhibitor-associated angioedema
- Cross-reactivity between ACE inhibitors and ARBs is small, but has been reported

7. Teratogenecity

- Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.
- When pregnancy is detected, discontinue as soon as possible.

8. Hyperkalemia

- The ACEI can increase serum potassium as a result of aldosterone reduction
- Potassium increases with ACEI monotherapy are very small and typically do not result in hyperkalemia.
  - CKD
  - ARBS/ aldosterone antagonists
  - Potassium supplements
  - Potassium-sparing diuretics
  - Direct renin inhibitor

Contraindications/precautions

- Pregnancy –C(2^{nd} and 3^{rd})
- History of angioedema
- Bilateral renal stenosis

Parameters To Monitor

- Serum electrolytes (especially creatinine and potassium)
- Symptoms of angioedema
- Blood pressure
- Symptoms of hypotension
- CBC (especially with captopril and enalapril) for neutropenia, which is more common in patients with preexisting renal impairment
- Cough

Angiotensin Receptor Antagonists

- ARBs bind to AT-II receptors in tissues preventing AT-II mediated vasoconstriction and aldosterone release thus ↓ BP
- Since ARBs do not block down the breakdown of bradykinins, do not cause cough
- The addition of low dose thiazide diuretics to an ARB significantly improves antihypertensive efficacy
- ARBs are beneficial in diabetic neuropathy/ albuminuria & can reduce renal complications in these patients
  - Used mostly when patients are allergic to ACEIs or intolerant due to cough
  - Decreased hyperkalemic effects compared to ACEIs
  - May cause angioedema (but rare)
  - Efficacy similar to other antihypertensives with fewer side effects
  - Contraindicated during pregnancy
  - More expensive than ACEIs and their effect on mortality risk is not well established

Angiotensin Receptor Antagonist

Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
Azilsartan (Edarbi)	40-80	1
Candesartan (Atacand)	8-32	1 or 2
Eprosartan (Teveten)	600-800	1 or 2
Irbesartan (Avapro)	150-300	1
Losartan (Cozaar)	50-100	1 or 2
Olmesartan (Benicar)	20-40	1
Telmisartan (Micardis)	20-80	1
Valsartan (Diovan)	80-320	1

Calcium Channel Blockers (CCBs)

- MOA: block inward mov't of calcium causing relaxation and dilation
- Two types -Dihydropyridines and Nondihydropyridines
- Dihydropyridines are potent vasodilators of peripheral/ coronary arteries
    - First-line agents for hypertension.
- Especially with coronary heart disease and diabetes.
- Nondihydropyridines decrease heart rate and slow atrioventricular nodal conduction.
- These drugs may also treat supraventricular tachyarrhythmias (e.g., atrial fibrillation).
- Baroreceptor mediated reflex tachycardia is more pronounced with the first generation dihydropyridines (e.g., nifedipine) and is significantly diminished with the newer agents (e.g., amlodipine) and when given in sustained-release dosage forms.
- In patients with hypertension and diabetes, dihydropyridine CCBs appear to be less cardioprotective than ACE inhibitors.

CCBs

- Efficacy of CCB may ↑ by adding a diuretic
- Very effective in older with ISHTN and black pts.
- May be more effective than ACEIs in preventing strokes
- Avoid IR CCBs, particularly nifedipine (used in HTN emergencies), due to possible serious S/E e.g. severe hypotension, cerebral ischemia, acute MI, conduction abnormalities and death
- **ADRs**
  - Dizziness, flushing, hypotension, headache, and peripheral edema due to vasodilation more likely with dihydropyridines
  - Gingival hyperplasia
  - Bradycardia or AV block = Diltiazem and verapamil
  - Constipation = 7% with verapamil and less likely with Diltiazem
- DI
  - Verapamil inhibit the cytochrome P450 3A4 isoenzyme system increase serum concentrations of cyclosporine, digoxin, lovastatin, simvastatin, tacrolimus, theophylline.
  - Nondihydropyridines with a β-blocker = Increased risk of heart block and HF

	Daily Dosage, mg	
	Low Dosage	Usual Dosage
Calcium channel blockers		
Nondihydropyridines		
Diltiazem	120	240–360
Verapamil	120	240–480
Dihydropyridines		
Amlodipine	2.5	5–10
Felodipine	2.5	5–10
Isradipine	2.5 twice daily	5–10 twice daily
Nifedipine	30	30–90
Nitrendipine	10	20

β-Blockers

- First-line agents to treat specific compelling indications (post-MI, coronary disease, heart failure).

Antihypertensive Mechanisms of **β-Blockers**

- Negative chronotropic and inotropic cardiac effects
- β_1- receptors on surface membranes of juxtaglomerular cells
- Decrease SNS outflow from CNS

○ Cardio selective (*Atenolol , Metoprolol, bisoprolol, nebivolol*)

- Non – selective (*Propranolol , Nadolol , Timolol*)
- ISA (*Acebutolol , Pindolol*)
- Mixed alpha & beta blockers (*Carvedilol , labetalol*)
- *Membrane stabilizing action*

	Daily Dosage, mg	
	Low Dosage	Usual Dosage
Atenolol	25	100
Bisoprolol	5	5–10
Carvedilol	3.125 twice daily	6.25–25 twice daily
Labetalol	100 twice daily	100–300 twice daily
Metoprolol succinate	25	50–100
Metoprolol tartrate	25 twice daily	50–100 twice daily
Nadolol	20	40–80
Nebivolol	2.5	5–10
Propranolol	40 twice daily	40–160 twice daily
Acebutalol	200	200–400

Side Effects

- Bradycardia, AV block and the development of acute heart failure.
- Cold extremities, exacerbation of PVD, Sexual dysfunction, Bronchospasm, Hypoglycemia

Abrupt cessation of β-blocker therapy can produce

✓ unstable angina, MI, or even death in patients with coronary disease.

✓ lead to rebound hypertension (a sudden increase in BP to above pretreatment values).

Always be tapered gradually over 1 to 2 weeks before eventually discontinuing the drug.

Central Alpha Agonists

- Clonidine: works rapidly in hypertensive emergencies
- Methyldopa (Aldomet®): used in pregnant women
- Side effects includes:
  - dry mouth, sensitivity reactions, orthostatic hypotension, rebound hypertension, dizziness, anxiety, perspiration, agitation & confusion
  - Sedation
  - Hepatotoxicity and hemolysis = methyldopa

Alternative Agents: α1-Blockers

- Prazosin, terazosin, and doxazosin
- Provide symptomatic benefits in men with BPH.

Side Effect

- "First-dose" phenomenon
  - Transient dizziness or faintness, palpitations, and even syncope within 1 to 3 hours of the first dose.
- Orthostatic hypotension
- Sodium and water retention can occur with chronic administration.
- Sexual dysfunction (priapism)

Alternative Agents: *Direct Arterial Vasodilators*

- Hydralazine, and minoxidil
- Relax arteriolar smooth muscle, ↓ perfusion pressure, and ↑ HR, ↑ cutaneous blood flow, ↓ systemic resistance
- Can cause fluid retention and tachycardia (↓ efficacy) & should be given with a diuretic (fluid retention), CCBs & beta blockers
- Useful in the management of severe or refractory hypertension
- Should be avoided in pts with ischemic heart disease (CAD), due to exacerbation of attack
- Side effects: edema, palpitations, flushing, headache
- Hydralazine: dose-dependent lupus-like syndrome
- Minoxidil: hypertrichosis (hirsutism),

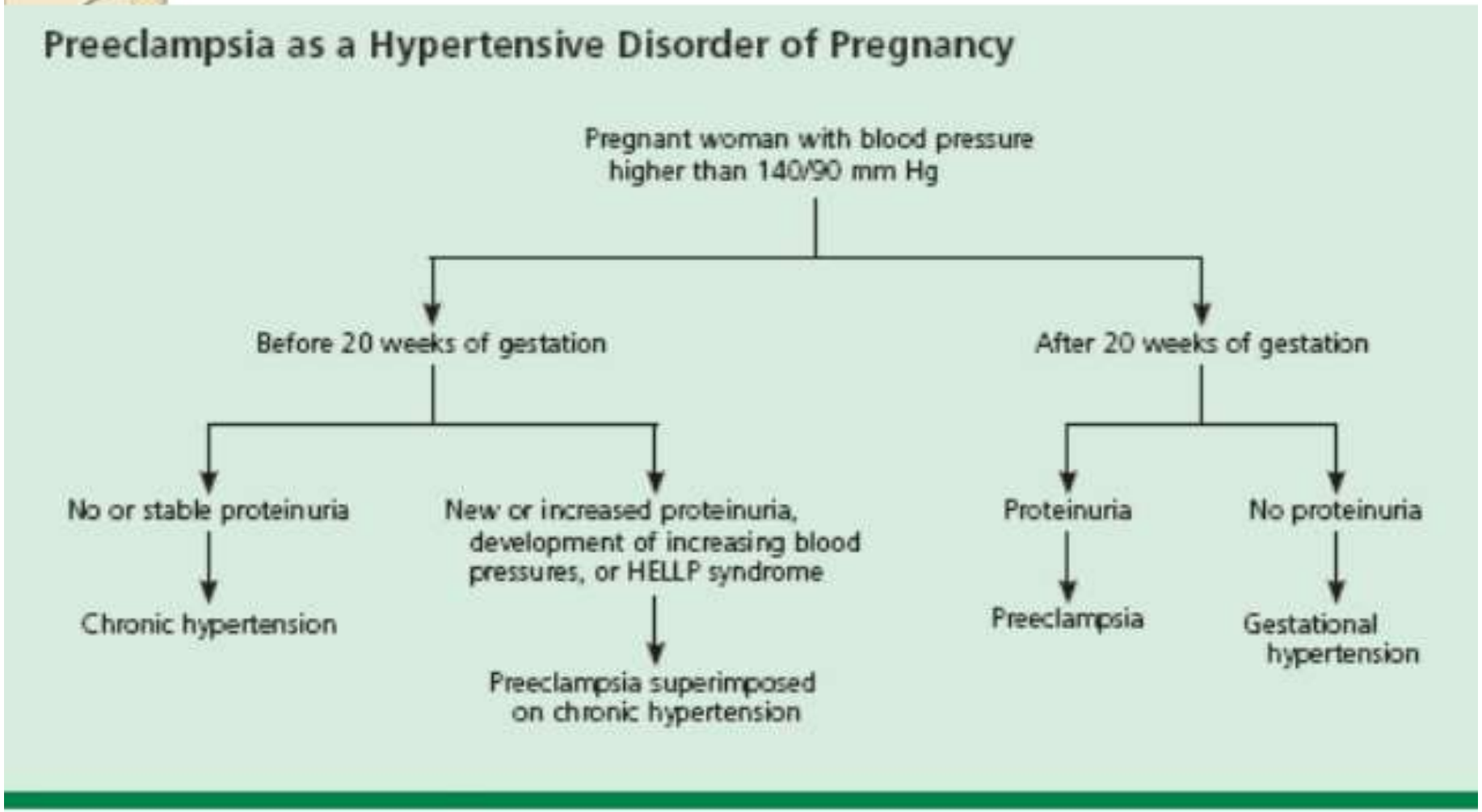


Figure 1. An algorithm for differentiating among hypertensive disorders in pregnant women (HELLP = *h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet count)

Treatment of Chronic Hypertension in Pregnancy

Drug/Class	Comments
Methyldopa	Long-term follow-up data supports safety; *considered a preferred agent*
β-Blocker	Generally safe, but intrauterine growth retardation reported (mostly with atenolol)
Labetalol	Increasingly used over methyldopa because of fewer side effects; *considered a first-line agent*
Clonidine	Limited data available; used mainly in third trimester
CCB	Limited data available; no increase in major teratogenicity with exposure (except immediate-release oral nifedipine should not be used); *long-acting nifedipine considered a preferred agent*
Thiazide	Not first-line agents but probably safe in low doses if started prior to conception for essential hypertension
ACEi, ARB, direct renin inhibitor	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)

- Labetalol, long-acting nifedipine, or methyldopa is recommended as first-line agents due to favorable safety profile
- Other β-Blockers (other than atenolol) and CCBs are also reasonable alternatives.

Drugs safe for the treatment of hypertension in pregnancy

- **B**etter — Beta blockers (labetalol and cardioslective except atenolol)
- **M**other — Mthyldopa (preferred drug)
- **C**are — Clondine
- **D**uring — Dihydropyridine CCB (sustained release nifedipine, amlodipine)
- **H**ypertensive — Hydralazine (DOC for hypertensive emergencies in pregnancy)
- **P**regnancy — Prazosin (and other alpha blockers)

- The classification of hypertensive urgencies and emergencies is determined **by the presence or absence of acute target-organ damage, not by BP**, and determines the appropriate treatment approach.
- The relative rise and rate of increase in BP is more important than the actual BP.

Hypertensive Urgencies and Emergencies

- Acute elevations of BP (> 180 mm Hg systolic or > 120 mm Hg diastolic) with the presence of acute or ongoing target organ damage **constitute a hypertensive emergency.**
- This situation requires immediate lowering of BP to prevent or minimize target organ damage.

Principles Of Treatment

- As an initial goal, reduce mean arterial pressure (MAP) by **no more than 25% within minutes to hours**.
  - Reach BP of 160/100 mm Hg within 2-6 hours.
- Further reduce BP toward normal over several weeks.
- Precipitous drops in BP may lead to end-organ ischemia or infarction.
- Measure BP every 5-10 minutes until goal MAP is reached and life-threatening target organ damage resolves.
- IV agents are preferred because of the ability to titrate dosages on the basis of BP response; however, specific agents should be chosen on the basis of patient findings.

Nitroprusside

- Potent vasodilator
- Direct vasodilatation on smooth muscle to decrease arterial pressure
- Usual rate of administration is 0.3-10mcg/kg/min
- **S/E:** reflex tachycardia, hypotension, cyanide toxicity with metabolite (prolonged use and high infusion rates)
- Useful in ischemic patients, however may worsen when rate > 2mcg/kg/min
- Effect enhanced by elevating the head of the pts bed
- Caution in renal or hepatic impairment pts
- ↓ CO & total peripheral resistance

Labetalol

- Alpha & Beta blocker
- Short onset and long duration of action
- Infusion is 0.5-2mg/min
- No chronotropic or inotropic effect on the heart
- Does not cause tachycardia
- Venous and arterial dilator & relaxes vascular smooth muscle
- Contraindicated in bronchial asthma pts & bradycardic pts
- Causes marked postural hypotension in intracranial hemorrhage pts

Nitroglycerin

- Dilates both arterial & venous vessels
- Decreases preload & afterload
- Increases blood supply to ischemic cardiac regions
- Used with HE associated coronary insufficiency
- Usual dose is 5-300mcg/min
- Pts may develop nitrate intolerance, so provide nitrate free intervals

Nicardipine

- CCB, so watch for S/E in that class
- Decreases afterload
- Short onset, with long duration of action
- Useful in coronary, or peripheral artery disease
- May cause tachycardia
- Use with caution in pts with coronary ischemia
- Usual dose is 5-15mg/hr

Enalaprilat

- ACEI so watch for S/E in that class
- Usual dose is 0.625-5mg IV Q6H
- Do not exceed 1.25mg/dose in renally impaired patients
- Useful in CHF & pts at risk for cerebral hypotension
- Avoid in acute MI or severe renal impairment pts

Hydralazine

- Vasodilator that ↓ peripheral vascular resistance by direct action on the vascular smooth muscle
- Usual dose is 5-40mg IV/IM Q4-6H
- Do not exceed 5mg/min IV push
- May cause lupus, reflex tachycardia, HA, dizziness, palpitations, joint pains
- Contraindicated in pts with aortic aneurysm or coronary artery disease
- Also used in pregnancy
- Many pts sensitive to parenteral doses due to hypotension

Hypertensive Emergency

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects	Special Indications
Sodium nitroprusside	0.25–10 mcg/kg/min intravenous infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure, azotemia, or in chronic kidney disease
Nicardipine hydrochloride	5–15 mg/h intravenous	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Clevidipine butyrate	1-2 mg/h intravenous infusion; may double dose every 90 sec initially; maximum: 32 mg/h; typical maintenance dose: 4 to 6 mg/h	2-4	5-15	Headache, syncope, dyspnea, nausea, vomiting	Most hypertensive emergencies except severe aortic stenosis; caution with heart failure
Fenoldopam mesylate	0.1–0.3 mcg/kg/min intravenous infusion	< 5	30	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

Hypertensive Emergency

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects	Special Indications
Nitroglycerin	5–100 mcg/min intravenous infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Hydralazine hydrochloride	12–20 mg intravenous 10–50 mg intramuscular	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache vomiting, aggravation of angina	Eclampsia
Labetalol hydrochloride	20–80 mg intravenous bolus every 10 min; 0.5–2.0 mg/min intravenous infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 mcg/kg/min intravenous bolus, then 50–100 mcg/kg/min intravenous infusion; may repeat bolus after 5 min or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure	Aortic dissection; perioperative

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

Monitoring Antihypertensives

Class	Parameters
Diuretics	blood pressure BUN/serum creatinine serum electrolytes (K+, Mg2+, Na+) uric acid (for thiazides)
β-Blockers	blood pressure heart rate
Aldosterone antagonists ACE inhibitors Angiotensin II receptor blockers	blood pressure BUN/serum creatinine serum potassium
Calcium channel blockers	blood pressure heart rate

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

Combination Therapy

- Most patients require ≥ 2 agents to control BP
- A thiazide-type diuretic should be one of these agents unless contraindicated
- Resistant hypertension: failure to achieve BP goal on full doses of 3 drug regimen including a diuretic

Hypertensive Urgencies

- Hypertensive urgencies are accelerated, malignant, or peri-operative elevations in blood pressure in the absence of new or progressive target organ damage;
  - Therefore, immediate lowering of BP is not required
  - Because rapid blood pressure reductions can cut off the supply of blood to the brain, leading to brain damage or death
- Moving the patient to a dark, quiet, calming environment
- One or more oral medicines (not IR nifedipine)
- Careful monitoring (every 15-30 minutes)

Agents Used to Treat Hypertensive Urgencies

Drug	Dose	Onset	Duration	Adverse effects
Captopril	25 mg, repeat in 1-2 hours as needed	5-15 min	4-6 h	Hypotension, acute renal failure, and angioedema
Clonidine	0.1-0.2 mg, repeat in 1-2 hours as needed (up to 0.6 mg)	5-15 min	6-12 h	Hypotension, drowsiness, sedation, and dry mouth
Labetalol	100-400 mg, repeat in 2-3 hours as needed	15-30 min	4-6 h	Hypotension, heart block, and bronchoconstriction

Introductory Case

- **Mr FH, a 48-year-old van driver, was identified by his general practitioner** (GP) as having a resting BP of 162/92 mmHg. He was in reasonably good health and purchased OTC ibuprofen 400 mg, which he took up to three times daily for arthritis-type pain when necessary. He weighed 95 kg, was 5'7" tall, and had a resting pulse rate of 82 beats per minute (bpm). He smoked 15 cigarettes per day and drank at least 6 units on 4 nights each week. His total cholesterol (TC) had been measured as 5.9mmol/L and his high-density lipoprotein (HDL) as 1.5 mmol/L (TC:HDL ratio 4.5).

Introductory Case

Q1. Why is it important to control blood pressure?

Q2. How would you assess Mr FH's cardiovascular disease (CVD) risk?

Q3. According to current guidelines, should Mr FH be treated for hypertension?

Q4. What non-drug approaches can Mr FH adopt to reduce his blood pressure and/or his cardiovascular (CV) risks, and why are these important?

Q5. What first-line treatments would be suitable for Mr FH's hypertension?

- A 64-year-old white male comes into your clinic with concerns about his BP. He arrived after his morning BP measurements at home were 149/90 mm Hg and when repeated 160/100 mm Hg. Upon examination in your clinic, seated BP in the left arm is 153/96 mm Hg and 157/89 mm Hg in the right arm. You request that the patient return to your clinic in 1 week for a follow-up BP. His seated BPs in the left arm 1 week later were 156/92 mm Hg and 150/87 mm Hg. The patient's physical examination was unremarkable, but his past medical history was significant for dyslipidemia and depression. His previous cholesterol panel revealed a high-density lipoprotein level of 52 mg/dL (1.34 mmol/L), triglyceride level of 180 mg/dL (2.03 mmol/L), and total cholesterol of 198 mg/dL (5.12 mmol/L). Calculated low-density lipoprotein level is 110 mg/dL (2.84 mmol/L). All other laboratory values were within normal limits. Current medications include aspirin and citalopram.
- Based on the information above,
- What stage of hypertension does this patient have?
- What is the patient's BP target according to ASH guidelines and by the evidence-based guidelines from the former JNC 8 panel?
- What steps are involved in assuring that the patient's BP measurements are accurate?

Case

- D.C. is a 44-year-old black man who presents to his primary care provider concerned about high BP. At an employee health screening last month, he was told he had hypertension. His medical history is significant for allergic rhinitis. His BP was 144/84 and 146/86 mm Hg last year during an employee health screening at work. D.C.'s father had hypertension and died of an MI at age 54. His mother had diabetes and hypertension and died of a stroke at age 68. D.C. smokes one pack per day of cigarettes and thinks his BP is high because of job-related stress. He does not believe that he really has hypertension. D.C. does not engage in any regular exercise and does not restrict his diet in any way, although he knows he should lose weight.
- Physical examination shows he is 175 cm tall, weighs 108 kg (body mass index [BMI] 35.2 kg/m2), BP is 148/88 mm Hg (left arm) and 146/86 mm Hg (right arm) while sitting, and heart rate is 80 beats/minute. Six months ago, his BP values were 152/88 mm Hg and 150/84 mm Hg when he was seen by his primary care provider for allergic rhinitis. Funduscopic examination reveals mild arterial narrowing and arteriovenous nicking, with no exudates or hemorrhages. The other physical examination findings are essentially normal.

Case…

- D.C.’s fasting laboratory serum values are as follows:
- Blood urea nitrogen (BUN), 24 mg/dL
- Creatinine, 1.0 mg/dL
- Glucose, 105 mg/dL
- Potassium, 4.4 mEq/L
- Uric acid, 6.5 mg/dL
- Total cholesterol, 196 mg/dL
- Low-density lipoprotein cholesterol (LDL-C), 141 mg/dL
- High-density lipoprotein cholesterol (HDL-C), 32 mg/dL
- Triglycerides, 170 mg/dL
- An electrocardiogram (ECG) is normal except for left ventricular hypertrophy (LVH).

Why does D.C. have hypertension?

- What is the proper assessment of D.C.'s BP?

- Which hypertension-associated complications are present in D.C.?

What other forms of hypertension-associated complications is D.C. at risk for?

Which major CV risk factors are present in D.C.?

- What is D.C.’s BP goal?
- What are the goals of treating D.C.?
- What patient education should be provided to D.C. regarding his hypertension?

Pharmacotherapy of Heart Failure

Learning objectives

- **Upon Completion of the unit, the students Will be able to:**
  - Differentiate between the common underlying etiologies of HF
  - Describe the pathophysiology of HF
  - Identify signs and symptoms of HF and classify a given patient by NYHA-FC/ACC/AHA HF Staging
  - Describe the goals of therapy for a patient with HF
  - Develop a nonpharmacologic treatment plan which includes patient education for managing HF
  - Develop a specific evidence-based pharmacologic treatment plan for a patient with acute or chronic HF based on disease severity and symptoms
  - Formulate a monitoring plan for the nonpharmacologic and pharmacologic treatment of a patient with heart failure.

Definition

- Heart failure (HF) is defined as the inadequate ability of the heart to pump enough blood to meet the blood flow and metabolic demands of the body.
- It is;
  - A progressive clinical syndrome that can result from any abnormality in **cardiac structure or function** that **impairs** the ability of the **ventricle to fill** with or **eject** blood.
  - Thus rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body.
- It is the final common pathway for numerous cardiac disorders, including those affecting the **pericardium, heart valves,** and **myocardium.**
- Diseases that adversely affect ventricular systole (contraction), ventricular diastole (filling) or both can lead to heart failure.

Epidemiology

- Epidemic particularly those aged 65 and older.
- 75-80% of the group > 65 years; prevalence of about 10% in people age 80 or older
- Affects about 6 million people in the US; or about 1.7% of the overall population
  - 800,000 new cases each year
- 2:1 ratio men: women
- Prognosis for patients with this disorder remains grim
- After diagnosis 20 % die w/in 1 yr. 50% within 5 yr.
- CHF is the leading cause of hospitalization in elderly patient
- Responsible for >11 million visits to a physician's office and result in 3.5 million hospitalizations per year
- Each year, 250,000 people die from CHF
- Annually, $25-50 billion
- The cost of hospitalization for CHF is twice that for all forms of cancer; most costly diseases in the United States with an estimated annual cost of over $4 billion.

Epidemiology…

- Average hospital length of stay is estimated to be between 4 to 6 days, a number which has remained constant over the past decade.
- The in-hospital mortality rate has been estimated at approximately 4%, but ranges from 2% to 20% depending on the report
- Readmissions are also high, with up to 30% to 60% of patients
- Readmitted within 6 months of their initial discharge date
- The 5-year mortality rate for chronic HF remains greater than 50%.
- Survival strongly correlates with severity of symptoms and functional capacity.
- Sudden cardiac death is the most common cause of death, occurring I approximately 40% of patients with HF.

Classification and Etiology: Low-Output Versus High-Output Failure

- Described as either low-output or high-output failure, with a predominance (>90%) of cases being low-output failure
  - In both types, the heart cannot provide adequate blood flow (tissue perfusion) to meet the body's metabolic demands, especially during exercise.
- The hallmark of classic low-output HF is a diminished volume of blood being pumped by a weakened heart in patients who have otherwise normal metabolic needs.

Low-Output Versus High-Output Failure…

- In high-output failure, the heart itself is healthy and pumps a normal or even higher than normal volume of blood.
  - Because of high metabolic demands caused by other underlying medical disorders (e.g., hyperthyroidism, anemia), the heart becomes exhausted from the increased workload and eventually cannot keep up with demand.
- The primary treatment of high-output HF is amelioration of the underlying disease.

- Low-output HF is further divided into;
  - Left and right ventricular dysfunction, or
  - A combination of the two (biventricular failure)
- When the left side of the heart fails, then fluid collects in the lungs (pulmonary edema)
  - Difficult for airways to expand
  - Breathing difficulty (Dyspnea, orthopnea, PND).
  - SOB (with activity or lying down)
- When the right side of heart fails, the fluid collects in the feet and lower legs; may also progress to abdomen causing ascites.
  - Pitting edema is when pressing down with fingers leaves an imprint.

- Left ventricular dysfunction is further subdivided into systolic and diastolic dysfunction, with mixed disorders also being encountered.
- **Systolic HF**
  - When the pumping action of heart is reduced or weakened. Also, there is an increase in wall stress.
  - EF (ejection fraction) is a common clinical measurement
    - When value is >50-60%--normal
    - If its <50% then most likely Heart Failure
    - It is a measure of how much blood is ejected out of the left ventricles (stroke volume) divided by maximum volume remaining in left ventricle after diastole.
  - In SHF, decrease in ejection fraction results in decrease in stroke volume and cardiac output
    - Leading to/ precipitating right ventricular failure and systemic venous hypertension.

- **Diastolic HF**
  - The heart can contract but it has less compliance; thus it is stiff.
  - This decreases proper filling of blood in the heart causing it to back up in the lungs.
  - EF is normal or slightly abnormal
  - According to studies:
    - It has been reported that statin therapy has potential to decrease mortality of patients with DHF.

SYSTOLIC VS DIASTOLIC FAILURE

Systolic failure:

- The inability of the ventricle to contract normally and expel sufficient blood

⇓

Inadequate cardiac output

⇓

Symptoms of hypoperfusion

- Weakness,

- Fatigue,

- Reduced exercise tolerance, & etc.

LVEF is *<40%, dropping to <20% in advanced HF*

Diastolic failure:

- Inability of the ventricle to relax and/or fill normally

⇓

- Manifestations relate principally to the elevation of filling pressures.

cardiac muscle function (contractility) is *not impaired and, most importantly,* the EF remains ≥45%

- **Many pts, have both ventricular hypertrophy *and* dilatation**

⇓

- Exhibit abnormalities both of contraction & relaxation

Classification and Etiology

Type of Failure	*Characteristics*	*Contributing Factors*	*Etiology*
Low output, systolic dysfunction (dilated cardiomyopathy)a (60%–70% of cases)	Hypofunctioning left ventricle; enlarged heart (dilated left ventricle); ↑left ventricular end-diastolic volume; EF <40%; ↓stroke volume; ↓CO; S_3 heart sound present	1. ↑Contractility (cardiomyopathy) 2. ↓Afterload (elevated SVR)	1. Coronary ischemia,b MI, mitral valve stenosis or regurgitation, alcoholism, viral syndromes, nutritional deficiency, calcium and potassium depletion, drug induced, idiopathic 2. Hypertension, aortic stenosis, volume overload

Low output, diastolic dysfunction (30%–40% of cases)	Normal left ventricular contractility; normal size heart; stiff left ventricle; impaired left ventricular relaxation; impaired left ventricular filling; ↓left ventricular end-diastolic volume; normal EF; ↓SV; ↓CO; exaggerated S_4 heart sound	1. Thickened left ventricle (hypertrophic cardiomyopathy) 2. Stiff left ventricle (restrictive cardiomyopathy) 3. ↑Preload	1. Coronary ischemia,b MI hypertension, aortic stenosis and regurgitation, pericarditis, enlarged left ventricular septum (hypertrophic cardiomyopathy) 2. Amyloidosis, sarcoidosis 3. Sodium and water retention
High-output failure (uncommon)	Normal or ↑contractility; normal size heart; normal	↑Metabolic and oxygen demands	Anemia and hyperthyroidism

Right vs. left heart failure

Right -sided

- Is relatively uncommon
- Results from diseased right ventricle
- Blood backs up into right atrium and venous circulation
- Peripheral congestion

Left-sided

- Most common form
- Blood backs up through the left atrium into the pulmonary veins
  - Pulmonary congestion and edema

Causes

- Weakened heart muscle
  - Damage can be from **coronary artery disease** leading to myocardial infarction or long lasting **high blood pressure**
  - MI leads to reduction in muscle mass and muscle stiffness
- Damaged heart valve
    - Stenotic valve- valve that does not open properly
    - Incompetent valve- valve that does not close properly causing fluid accumulation in lungs and body
    - IV drug use
- Blocked blood vessels supplying heart muscles
- Long lasting high blood pressure which may lead to left ventricular hypertrophy

Causes…

- Congenital heart disease
- Prolonged severe arrythmias
- Pericardial disease (pericardial effusion)
- Sometimes cause is unknown
- Contributing factors (habits)
  - Alcohol
  - Smoking
  - Obesity →DM, hyperlipidemia
- Thyrotoxicosis
- Pregnancy
- Infective Endocarditis

TABLE 16-3 Drugs That May Precipitate or Exacerbate Heart Failure

Negative inotropic effect
Antiarrhythmics (e.g., disopyramide, flecainide, propafenone, and others)
β-Blockers (e.g., propranolol, metoprolol, atenolol, and others)
Calcium channel blockers (e.g., verapamil, diltiazem)
Itraconazole
Terbinafine
Cardiotoxic
Doxorubicin
Daunomycin
Cyclophosphamide
Trastuzumab
Imatinib
Ethanol
Amphetamines (e.g., cocaine, methamphetamine)
Sodium and water retention
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Rosiglitazone and pioglitazone
Glucocorticoids
Androgens and estrogens
Salicylates (high dose)
Sodium-containing drugs (e.g., carbenicillin disodium, ticarcillin disodium)

Pathogenesis

- When the heart begins to fail, the body activates several complex compensatory mechanisms in an attempt to maintain CO and oxygenation of vital organs.
- These include;
  - Increased sympathetic tone (tachycardia and increased contractility)
  - Activation of the RAAS
  - Sodium and water retention (increased preload)
  - Other neurohormonal adaptations, and
  - Cardiac "remodeling" (ventricular dilation, cardiac hypertrophy, and changes in left ventricular lumen shape).
- The long-term consequences of these adaptive mechanisms can create more harm than good, however.

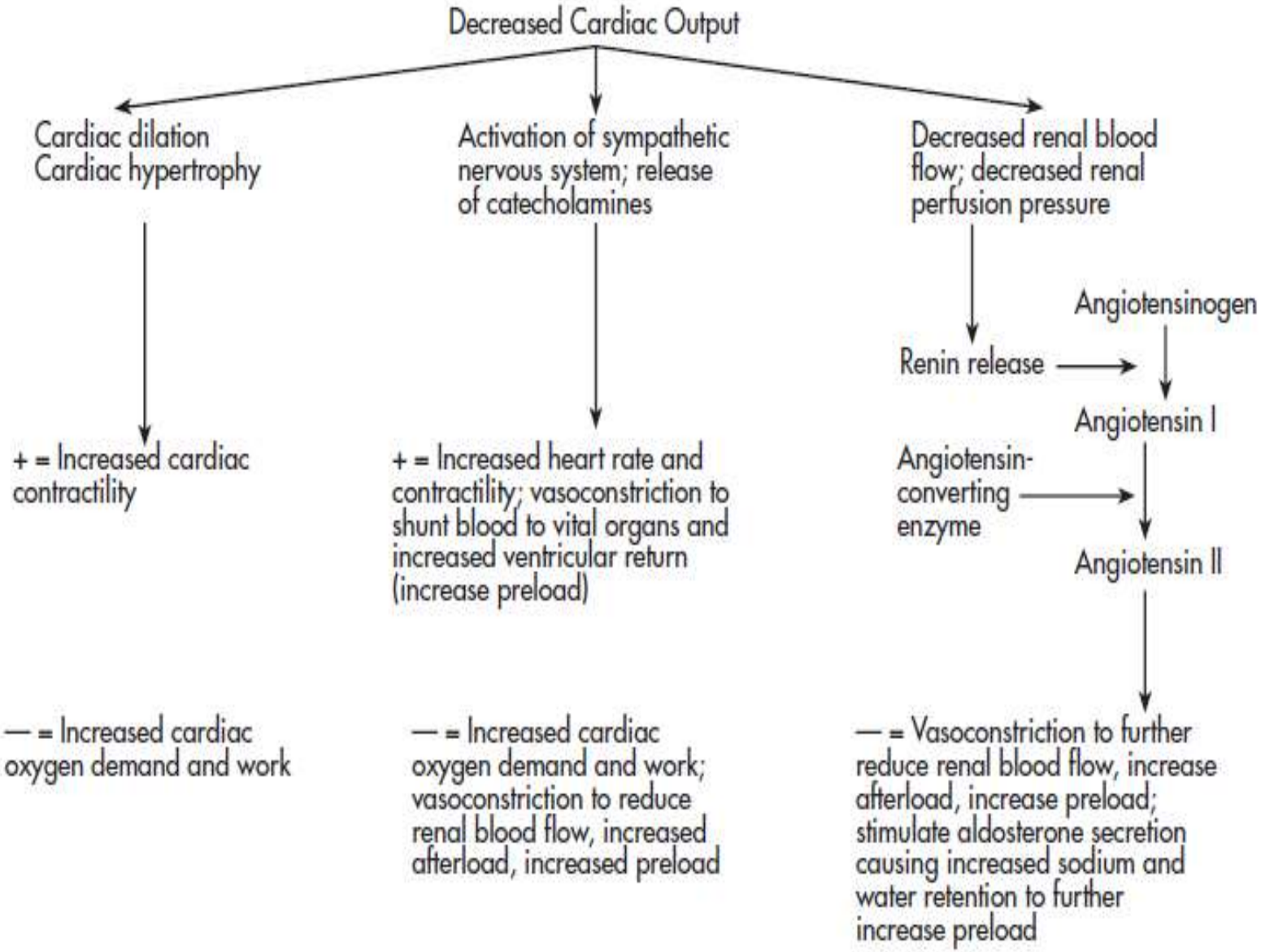
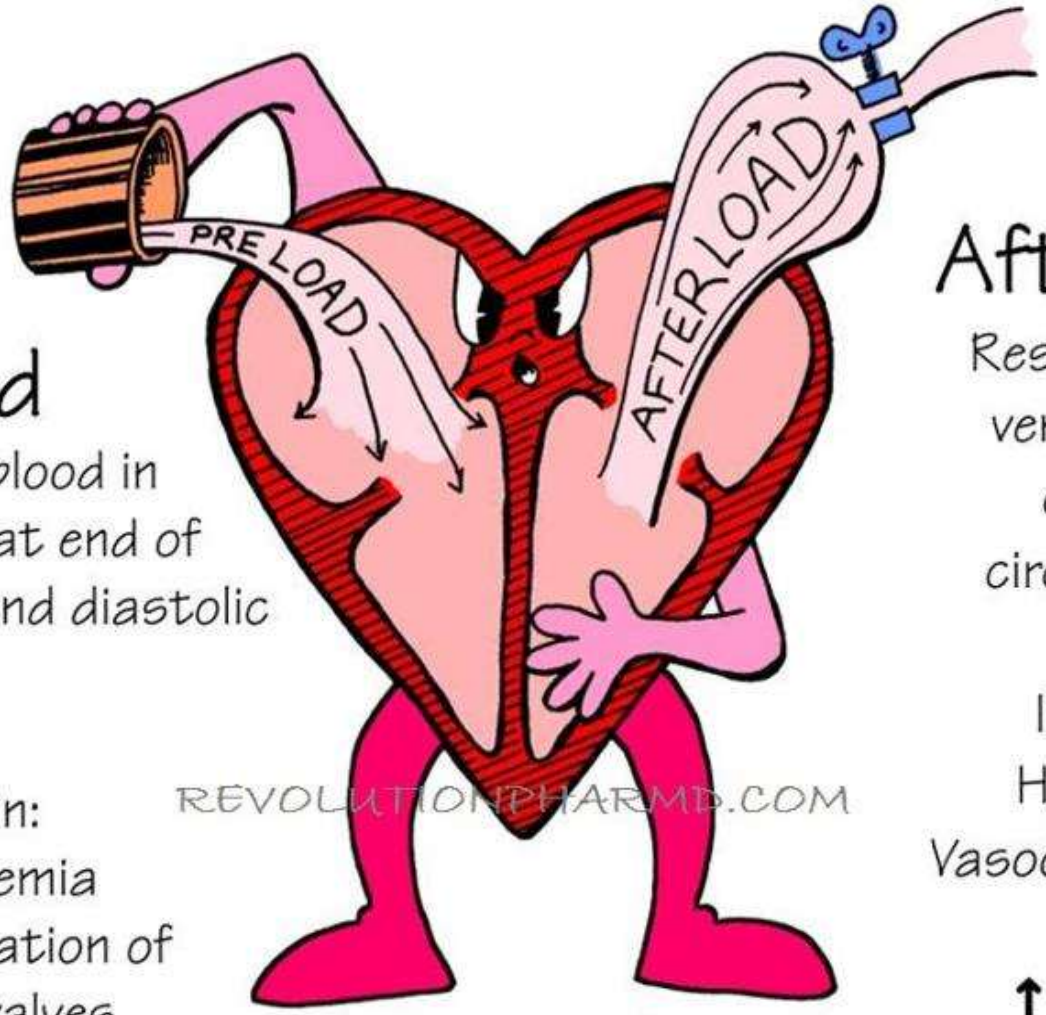


FIGURE 18-1 Adaptive mechanisms in systolic heart failure (HF). +, beneficial results; –, negative (detrimental) effects.

Compensatory Responses in HF

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through Na^+ & water retention)	Optimize stroke-volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO_2
Vasoconstriction	Maintain BP in face of reduced CO Shunt blood from nonessential organs to brain and heart	Increased MVO_2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (because of SNS activation)	Helps maintain CO	Increased MVO_2 Shortened diastolic filling time β_1-receptor downregulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular hypertrophy and remodeling	Helps maintain CO Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death Increased risk of myocardial ischemia Increased arrhythmia risk Fibrosis

PRELOAD AND AFTERLOAD



Preload

Volume of blood in ventricles at end of diastole (end diastolic pressure)

Increased in:

- Hypervolemia
- Regurgitation of cardiac valves
- Heart Failure

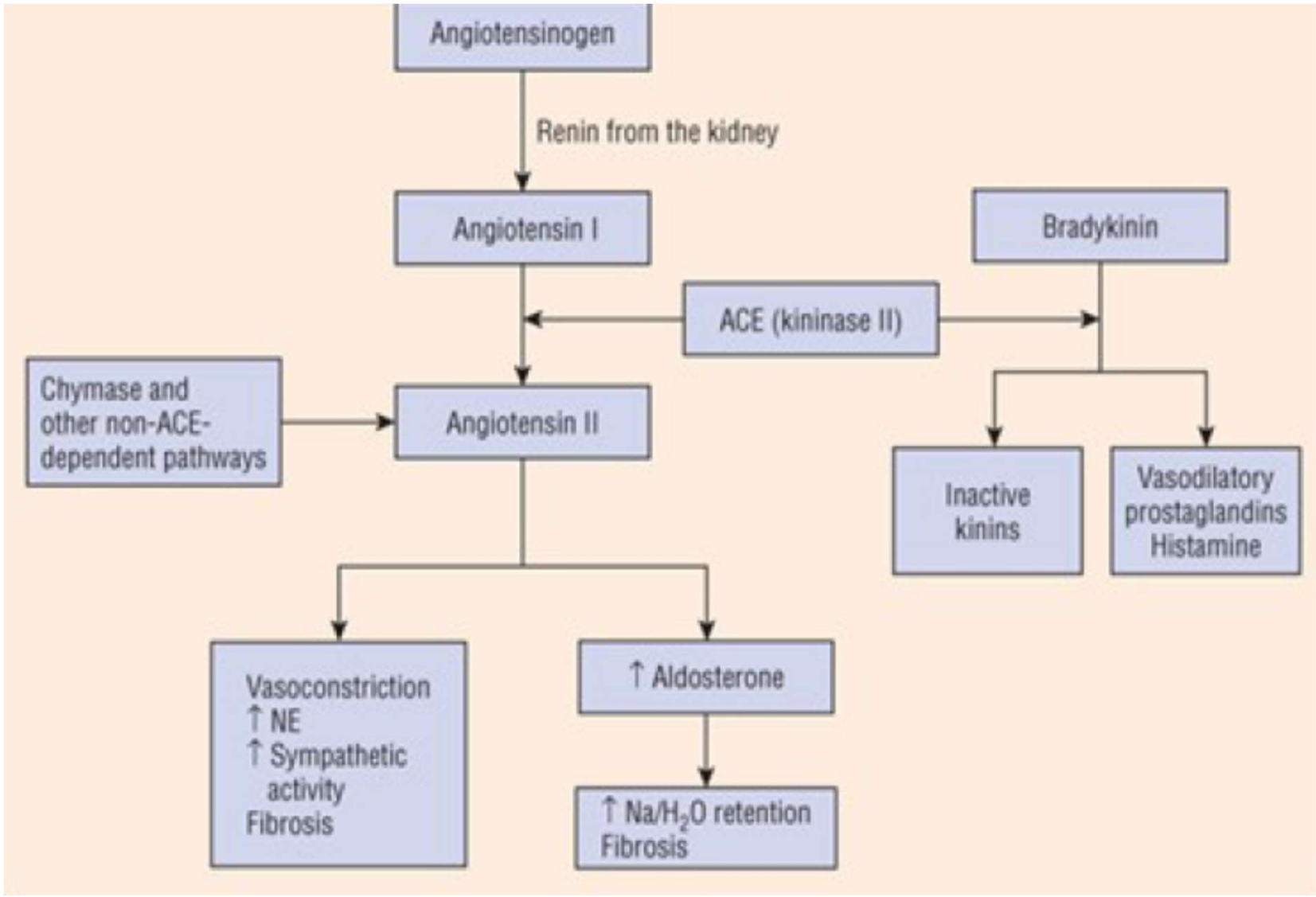
Afterload

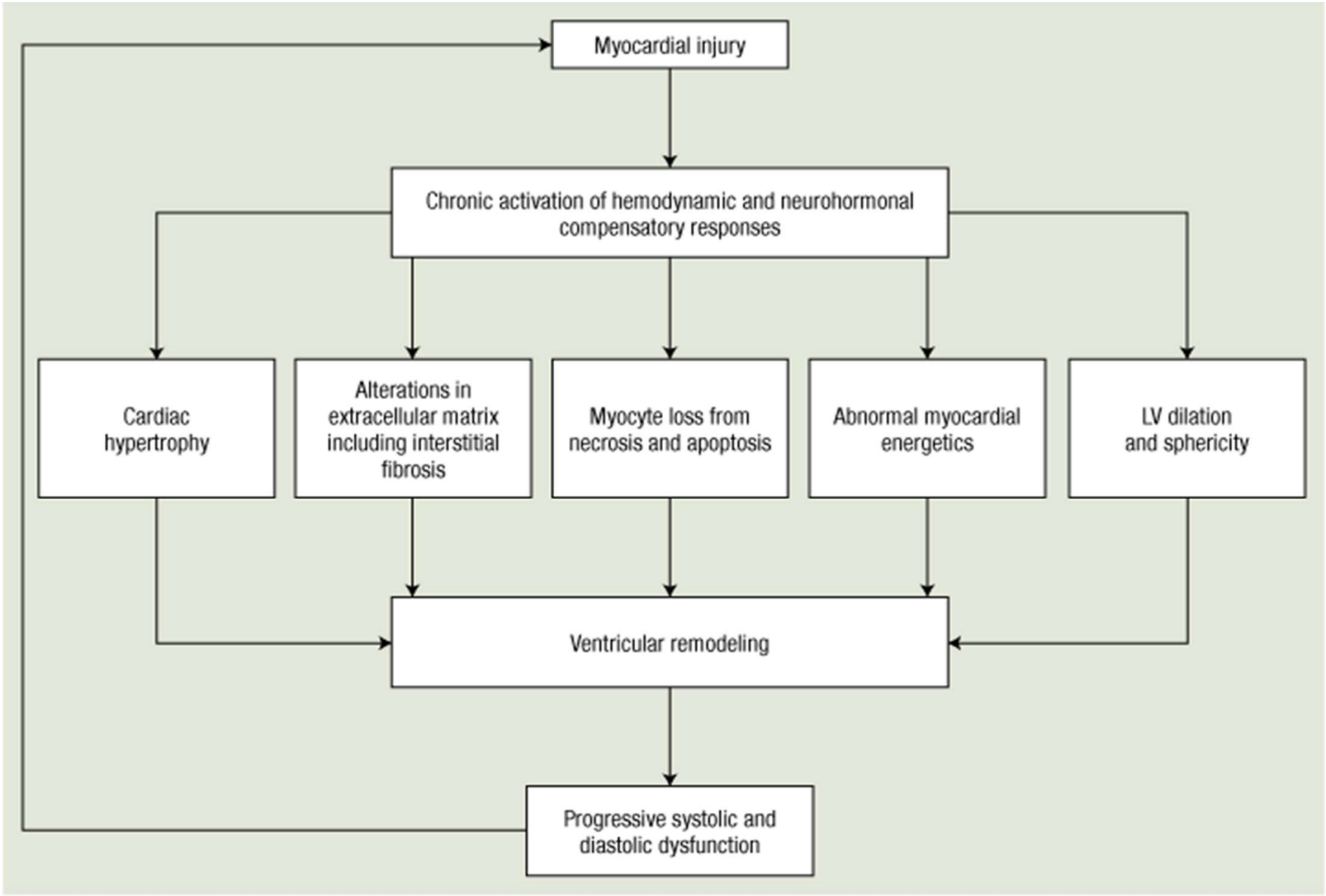
Resistance left ventricle must overcome to circulate blood

Increased in:

Hypertension
Vasoconstriction

↑ Afterload =
↑ Cardiac workload


Angiotensinogen
Renin from the kidney
Angiotensin I
Bradykinin
ACE (kininase II)
Chymase and other non-ACE-dependent pathways
Angiotensin II
Inactive kinins
Vasodilatory prostaglandins Histamine
Vasoconstriction
↑ NE
↑ Sympathetic activity
Fibrosis
↑ Aldosterone
↑ Na/H2O retention
Fibrosis



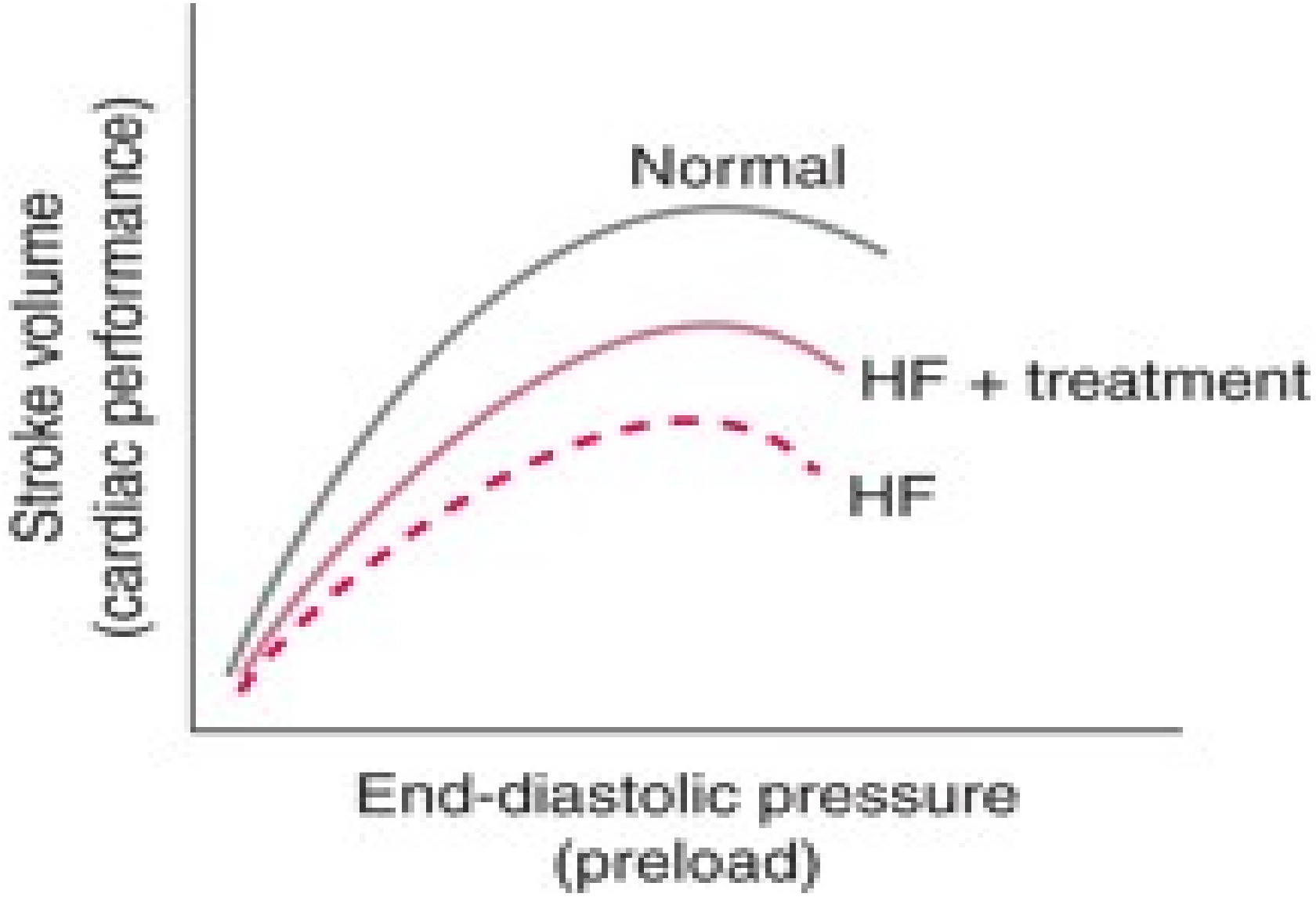
DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

Compensatory mechanisms

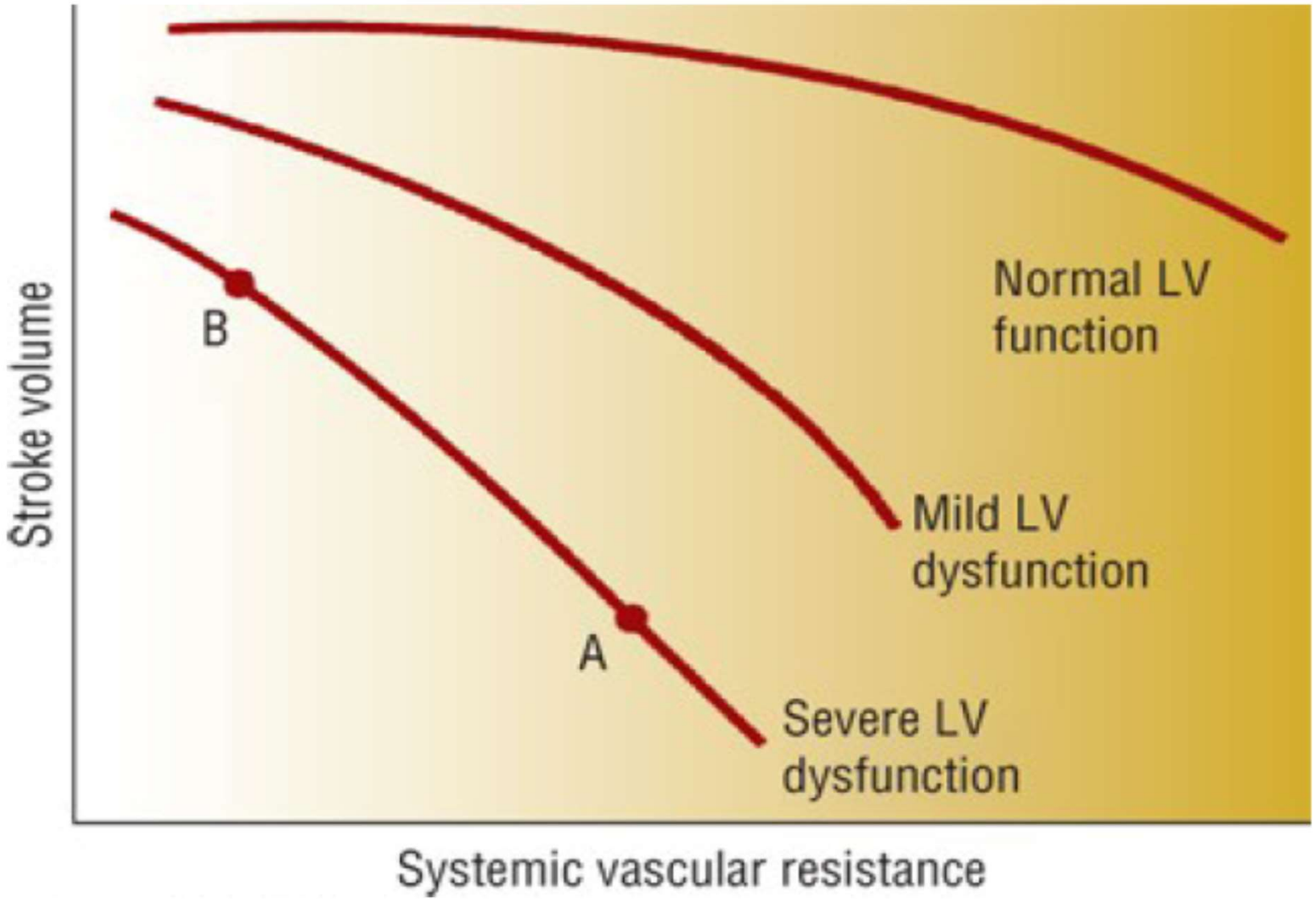
- Compensated heart failure vs. *Decompensated heart failure*

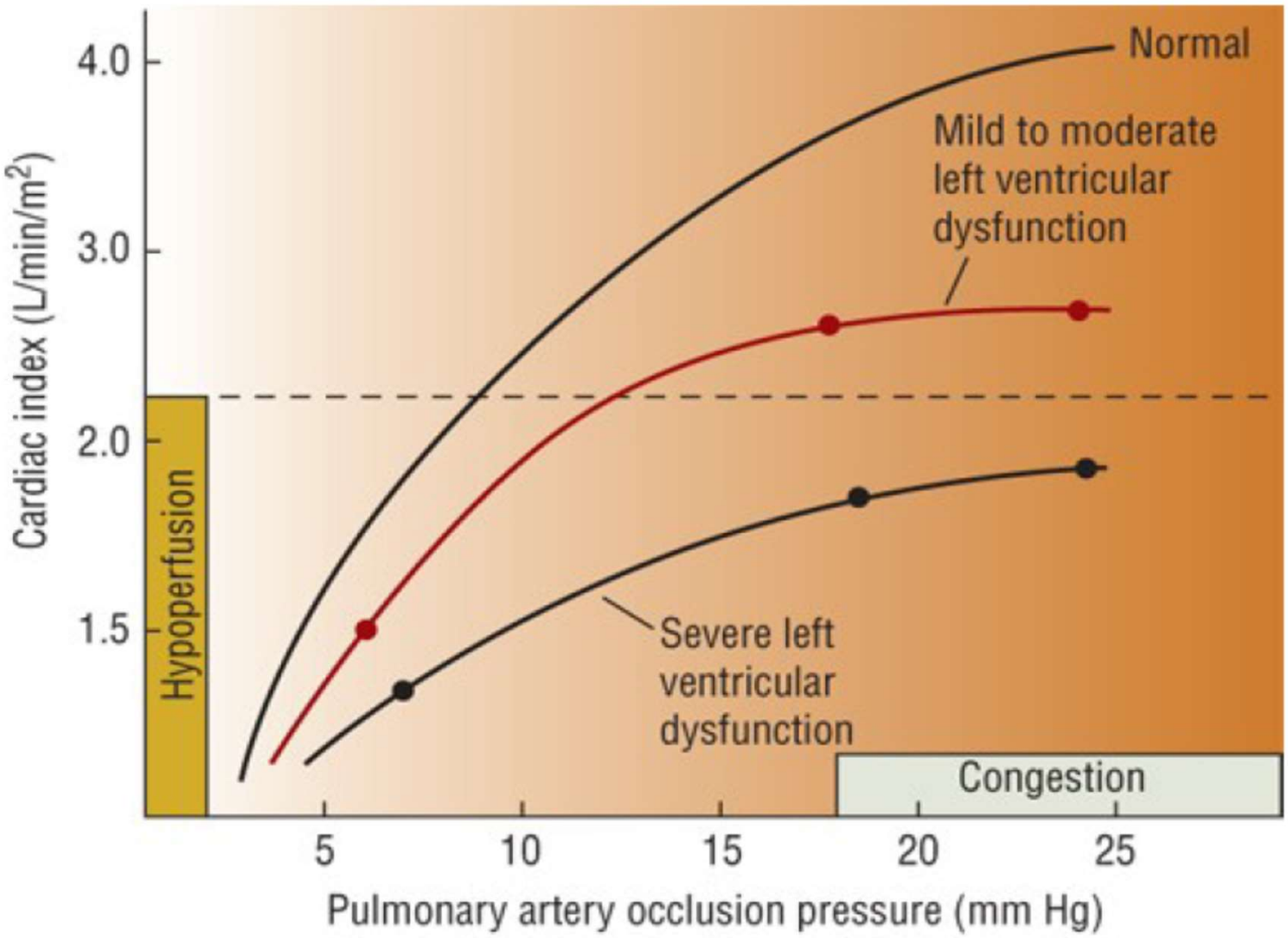
Frank-Starling Principle

- Normally (top curve), as preload increases, cardiac performance also increases. However at a certain point, performance plateaus, then declines.
- In heart failure (HF) due to systolic dysfunction (bottom curve), the overall curve shifts downward, reflecting reduced cardiac performance at a given preload, and as preload increases, cardiac performance increases less.
- With treatment (middle curve), performance is improved, although not normalized.


Stroke volume
(cardiac performance)
Normal
HF + treatment
HF
End-diastolic pressure
(preload)

As the extent of LV dysfunction increases, the negative, inverse relationship between stroke volume and systemic vascular resistance becomes more important.




Normal
Mild to moderate left ventricular dysfunction
Severe left ventricular dysfunction
Hypoperfusion
Congestion
Cardiac index (L/min/m²)
4.0
3.0
2.0
1.5
5
10
15
20
25
Pulmonary artery occlusion pressure (mm Hg)

Clinical Presentations

- In low-output HF, symptoms are generally related to either;
  - Congestion behind the failing ventricle(s), or
  - Hypoperfusion (decreased tissue blood supply), or both.

Clinical features of left heart failure

Symptoms

- Reduced exercise capacity
- Dyspnea (wheeze, orthopnea, PND)
- Cough (haemptysis)
- Lethargy and fatigue
- Reduced appetite and weight loss
- Mental status changes
- Cachexia

Signs

- Cool skin
- Displaced apex
- S_3 gallop
- Mitral regurgitation
- Pulmonary crepitations
- Pulmonary rales
- $\pm$ Pleural effusion

Clinical features of right heart failure

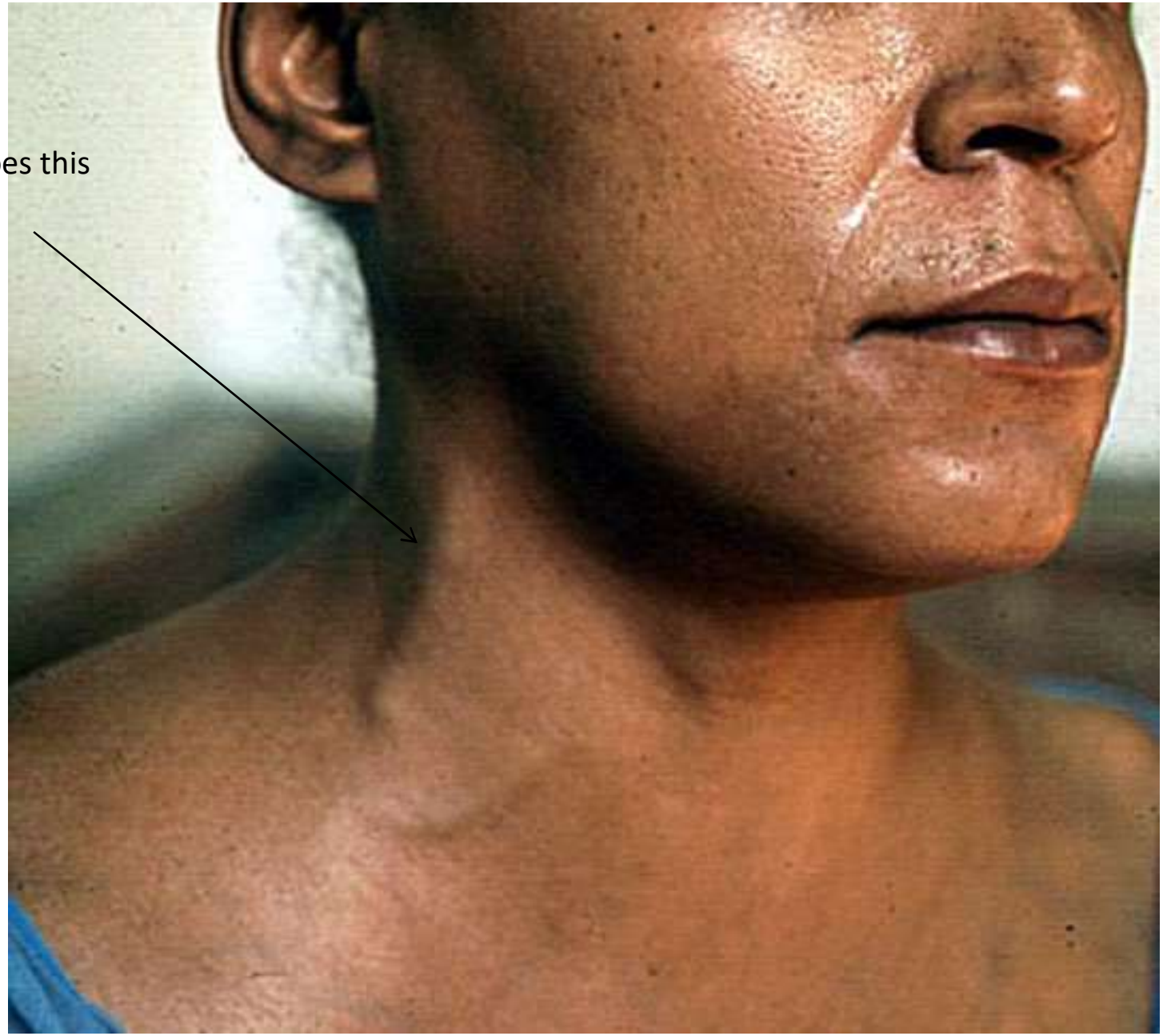
Symptoms

- Exercise intolerance
- Anorexia
- Nausea
- Bloating
- Ascites

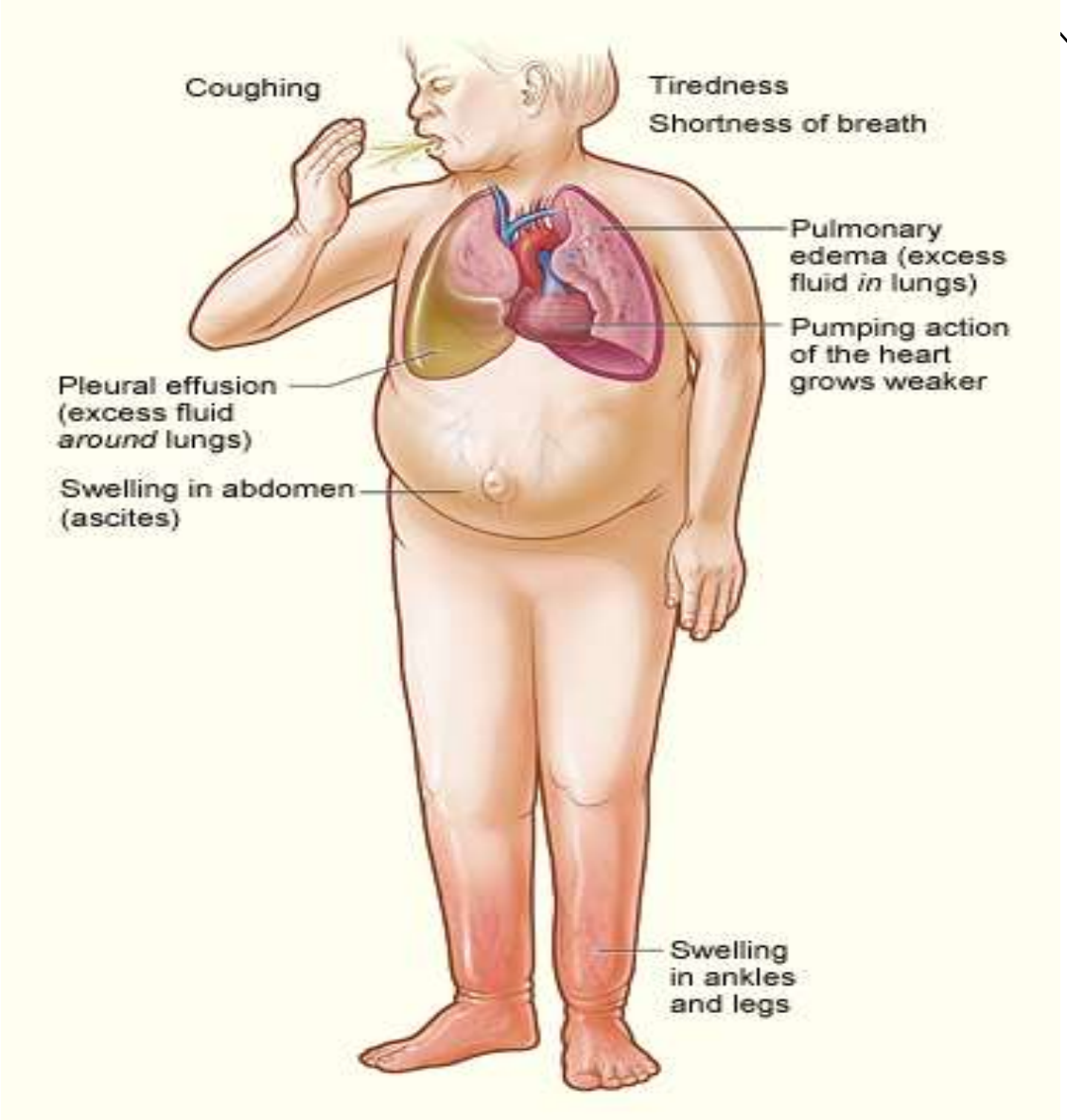
Signs

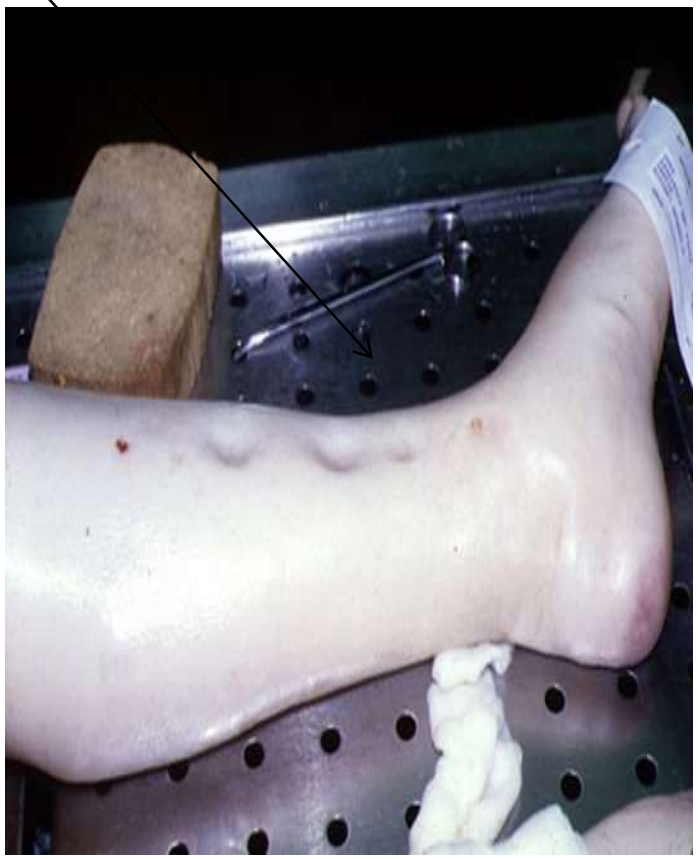
- Cardiomegaly
- Peripheral edema (e.g., pedal edema, which is swelling of feet and ankles)
- Jugular venous distension (JVD)
- **Hepatojugular reflex** (HJR)
- Hepatomegaly

What does this show?



What is present in this extremity, common to right sided HF?



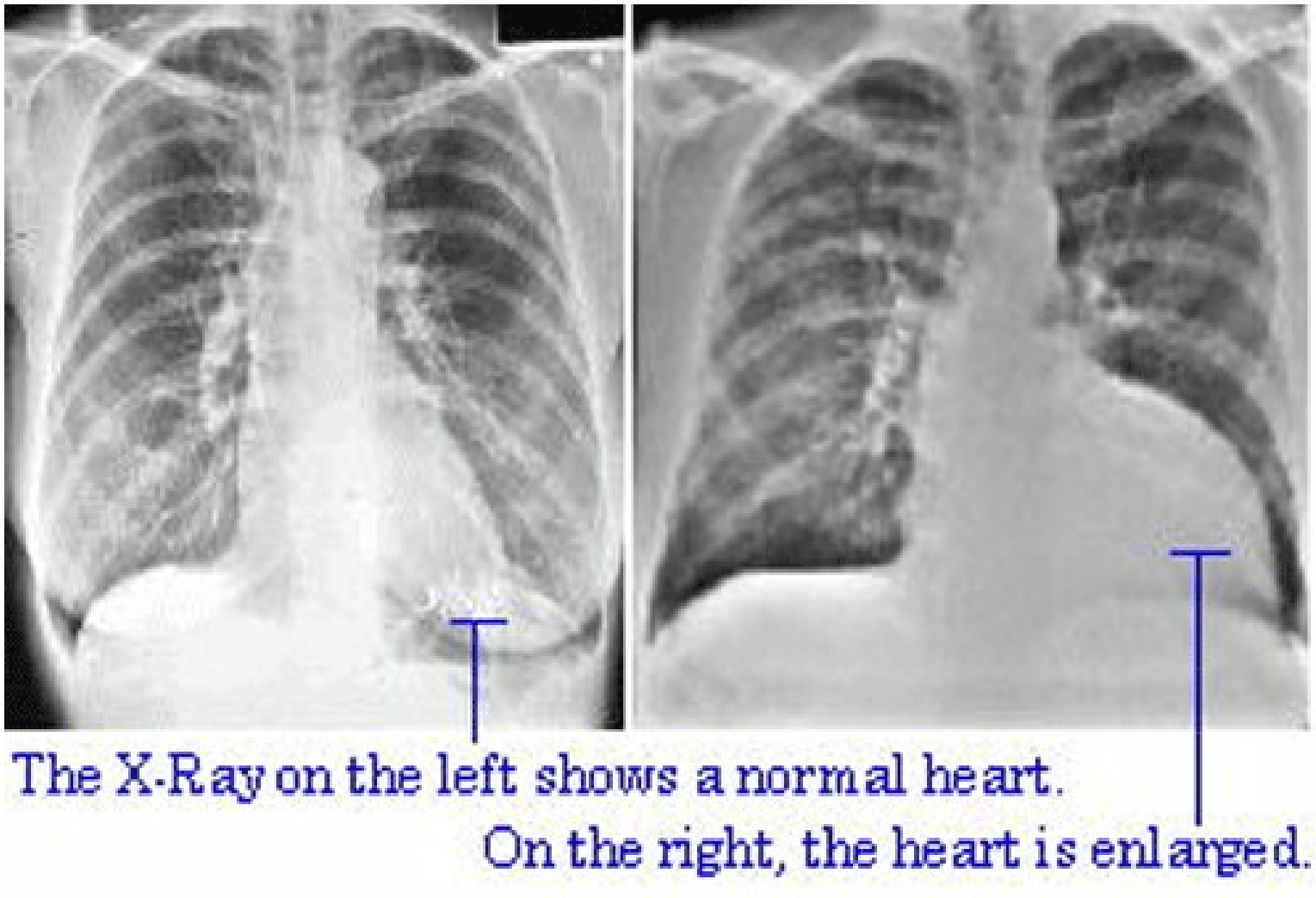


Grading of Pitting edema

- 1+: slight pitting/2 mm, disappears rapidly,
- 2+: somewhat deeper pit/4 mm, disappears in 10-15 sec
- 3+: deep pit/6 mm, may last > 1 minute; deep extremity swollen
- 4+: very deep pit/8 mm, lasts 2-5 min, deep extremity grossly distorted

Diagnostic Tests

- **Echocardiogram**
  - Ultrasound showing beating of heart and various cardiac structures
    - Determines cause of HF(muscle, valve, pericardium)
    - Provides EF which is the main distinguishing factor between DHF and SHF
- **CXR**
  - Useful for detection of **cardiac enlargement,** pulmonary edema, and pleural effusions
- **ECG**
  - Can reveal presence of heart attack, rhythm disorder, long lasting strain from high blood pressure or valve problems



Cardiomegaly/ventricular remodeling occurs as heart overworked> changes in size, shape, and function of heart after injury to left ventricle. Injury due to acute myocardial infarction or due to causes that inc. pressure or volume overload as in *Heart failure*

- **Blood Tests**
  - Sodium, potassium and other electrolytes
  - Renal, hepatic and thyroid function tests
  - **B-type natriuretic peptide (BNP)**
    - Hormone that is produced in higher levels by failing heart muscle
    - BNP < 35 pg/mL
    - N-terminal pro-BNP (NT-proBNP) < 125 pg/mL
    - Recommended for ruling-out HF, but not to establish the diagnosis
  - Lipid profile and
  - Hemoglobin A1C
  - Compete blood count (to determine if HF due to reduced oxygen-carrying capacity)
- **Stress Test**
  - Treadmill or medication
    - Evaluate cause of heart failure
    - Combined with other tests for accuracy

- A careful medication history should also be obtained.
- Particular attention should be paid to cardiovascular risk factors;
  - Such as hypertension, coronary artery disease, diabetes, dyslipidemia, tobacco use, sleep-disordered breathing, and thyroid disease.

Normal Values

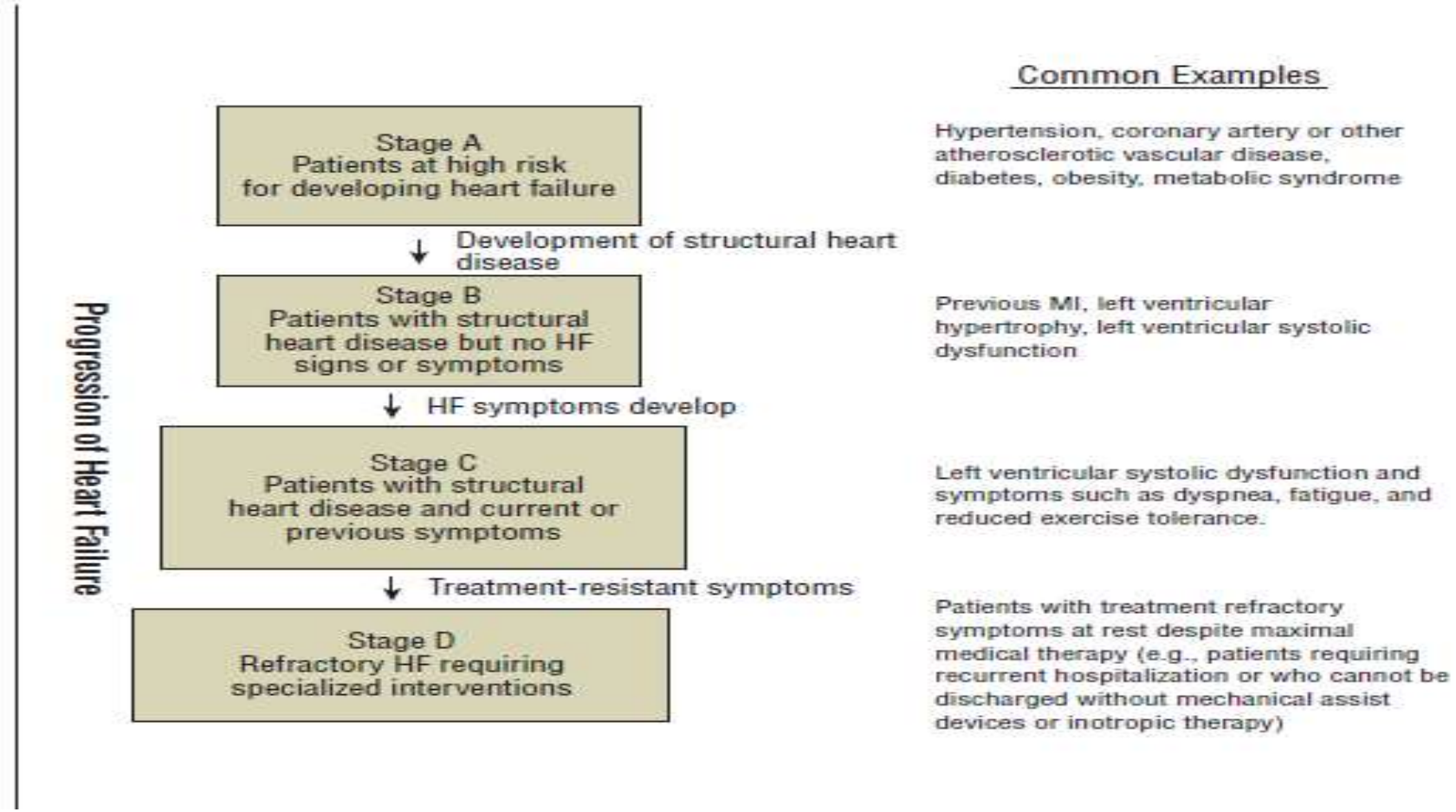
- Stroke Volume= (60-130ml)
- Cardiac Output=SV*HR=4-7 L/min
- Left ventricular ejection fraction (LVEF)= 60-70%

Classification

- The New York Heart Association (NYHA) Functional Classification System is intended primarily to classify symptomatic HF patients according to the physician's subjective evaluation.

New York Heart Association (NYHA) classification of functional status of the patient with heart failure	
I	No symptoms with ordinary physical activity (such as walking or climbing stairs)
II	Slight limitation with dyspnea on moderate to Severe exertion (climbing stairs or walking uphill)
III	Marked limitation of activity, less than ordinary activity causes dyspnea (restricting walking distance and limiting climbing to one flight of stairs)
IV	Severe disability, dyspnea at rest (unable to carry on physical activity without discomfort)

The American College of Cardiology/American Heart Association (ACC/AHA) staging system provides a more comprehensive framework for evaluating, preventing, and treating HF as follows;



NYHA Functional Class	ACC/AHA Stage	Description
N/A	A	Patients at high risk for heart failure but without structural heart disease or symptoms of heart failure.
I	B	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	C	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	C	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	C, D	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of heart failure are present at rest. With any physical activity, increased discomfort is experienced. Stage D refers to end-stage heart failure patients.

Desired Outcomes

- The therapeutic goals for chronic HF are:
  - Improve quality of life
  - Relieve or reduce symptoms
  - Prevent or minimize hospitalizations
  - Slow disease progression
  - Prolong survival
- The first step in managing chronic HF is to determine the etiology or precipitating factors.
  - Treatment of underlying disorders (e.g., anemia, hyperthyroidism) may obviate the need for treating HF.

- **Non-pharmacologic interventions include:**
  - Stop smoking
  - Loose weight
  - Avoid alcohol
  - Avoid or limit caffeine
  - Eat a low-fat, low-sodium diet (approximately 2 to 3 g of sodium per day).
  - Limit fluid intake (maximum 2 L/day from all sources)
  - Modest Exercise
  - Reduce stress
  - Keep track of symptoms and weight and report any changes or concern to the health care provider
  - Immunization against influenza and pneumococcus
  - Avoidance of medications that can exacerbate HF.

Drugs Used in Heart Failure

ACE INHIBITORS

Captopril
Enalapril
Fosinopril
Lisinopril
Quinapril
Ramipril

ARBs

Candesartan
Losartan
Telmisartan
Valsartan

Beta blockers

Bisoprolol
Carvedilol
Metoprolol

DIURETICS

Bumetanide
Furosemide
Torsemide
Metolazone

VASODILATORS

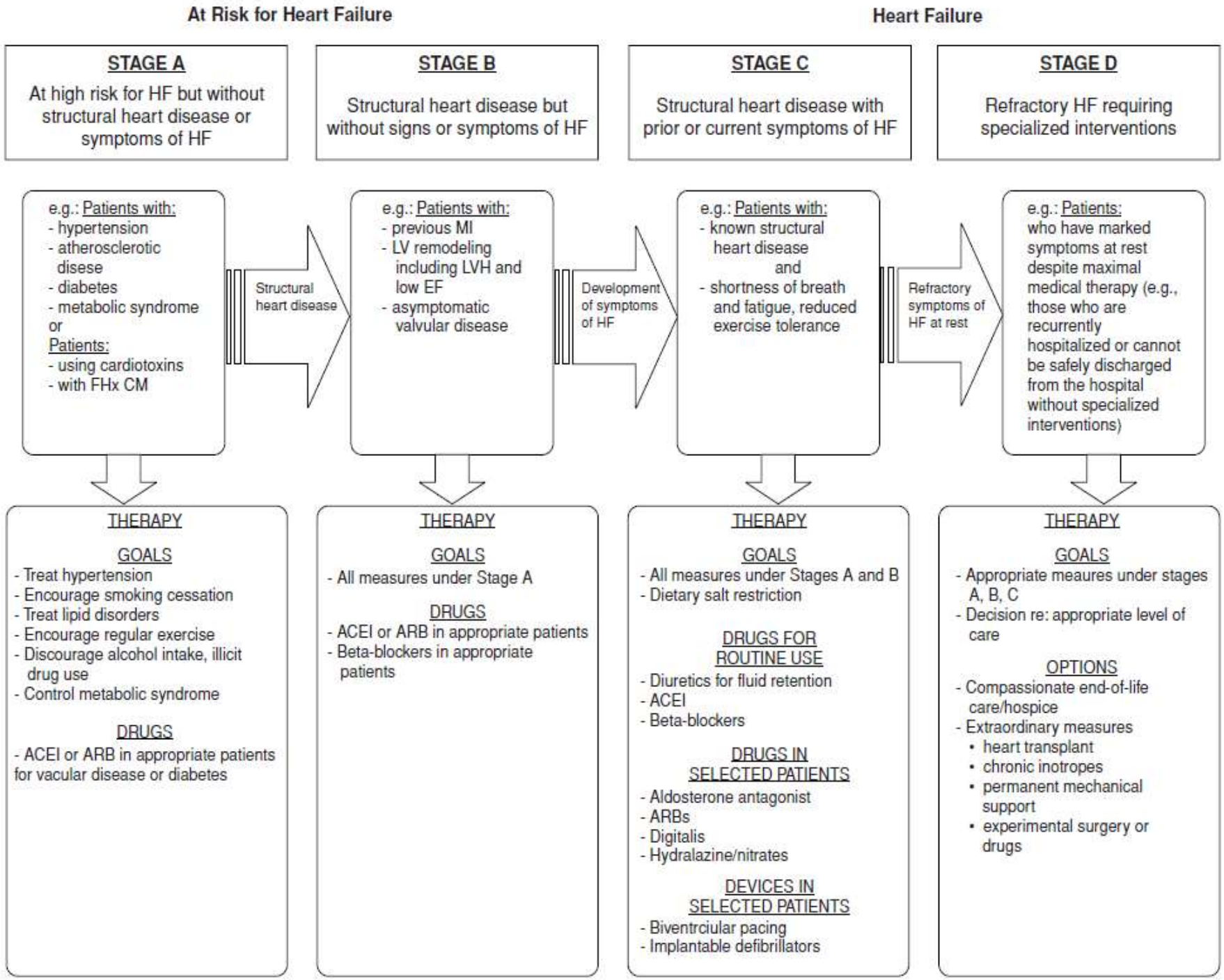
Hydralazine
Isosorbide dinitrate
Hydralazine/Isosorbide dinitrate

INOTROPIC AGENTS

Digoxin
Dobutamine
Dopamine
Milrinone
Inamrinone

ALDOSTERONE ANTAGONISTS

Eplerenone
Spironolactone


At Risk for Heart Failure
Heart Failure
STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
STAGE B
Structural heart disease but without signs or symptoms of HF
STAGE C
Structural heart disease with prior or current symptoms of HF
STAGE D
Refractory HF requiring specialized interventions
e.g.: Patients with:
- hypertension
- atherosclerotic disese
- diabetes
- metabolic syndrome
or
Patients:
- using cardiotoxins
- with FHx CM
Structural heart disease
e.g.: Patients with:
- previous MI
- LV remodeling including LVH and low EF
- asymptomatic valvular disease
Development of symptoms of HF
e.g.: Patients with:
- known structural heart disease
and
- shortness of breath and fatigue, reduced exercise tolerance
Refractory symptoms of HF at rest
e.g.: Patients:
who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
THERAPY
GOALS
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome
DRUGS
- ACEI or ARB in appropriate patients for vacular disease or diabetes
THERAPY
GOALS
- All measures under Stage A
DRUGS
- ACEI or ARB in appropriate patients
- Beta-blockers in appropriate patients
THERAPY
GOALS
- All measures under Stages A and B
- Dietary salt restriction
DRUGS FOR ROUTINE USE
- Diuretics for fluid retention
- ACEI
- Beta-blockers
DRUGS IN SELECTED PATIENTS
- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates
DEVICES IN SELECTED PATIENTS
- Biventrciular pacing
- Implantable defibrillators
THERAPY
GOALS
- Appropriate meaures under stages A, B, C
- Decision re: appropriate level of care
OPTIONS
- Compassionate end-of-life care/hospice
- Extraordinary measures
• heart transplant
• chronic inotropes
• permanent mechanical support
• experimental surgery or drugs

Stage A:

- The emphasis is on **identifying and modifying risk factors to prevent development of structural heart disease and subsequent HF.**
- Strategies include:
  - Smoking cessation and
  - Control of hypertension, diabetes mellitus and dyslipidemia according to current treatment guidelines.

- **ACEIs or ARBs** should be strongly considered for antihypertensive therapy in patients with multiple vascular risk factors.

Stage B:

- MI, LVH, valvular disease, reduced ejection fraction
- In these patients with structural heart disease but no symptoms, treatment is targeted at **minimizing additional injury and preventing or slowing the remodeling process.**

- In addition to treatment measures outlined for stage A, patients with a previous MI should receive both ACEIs or ARBs and β-blockers regardless of the ejection fraction.
  - Patients with reduced ejection fractions (less than 40%) should also receive both agents, regardless of whether they have had an MI.

Stage C:

- Most patients with structural heart disease and previous or current HF symptoms should receive the treatments for Stages A and B as well as:
  - initiation and titration of a diuretic (**if clinical evidence of fluid retention**)
  - ACE inhibitor and
  - β-blocker (if not already receiving a β-blocker for previous MI, left ventricular dysfunction, or other indication).
- If symptoms do not improve, the following drugs may be useful in carefully selected patients.
  - Aldosterone receptor antagonist
  - ARB (in ACE inhibitor-intolerant patients)
  - Digoxin and/or
  - Hydralazine/isosorbide dinitrate (ISDN)

Stage D:

- Patients with symptoms at rest despite maximal medical therapy should be considered for **specialized therapies** including:
  - Mechanical circulatory support
  - continuous intravenous positive inotropic therapy
  - cardiac transplantation or
  - hospice care

Pharmacologic Therapy of HFpEF

- **With a few notable exceptions,** many of the drugs used to treat HFrEF are the same as those for treatment of HFpEF.
- However, the rationale for their use, the pathophysiologic process that is being altered by the drug, and the dosing regimen may be entirely different depending on whether the patient has HFrEF or HFpEF.
- β-blockers are used to decrease HR, increase diastolic duration, and modify the hemodynamic response to exercise.
- In HFrEF, β-blockers are used in the long term to increase the inotropic state and modify LV remodeling.
- Diuretics also are used in the treatment of both HFrEF and HFpEF.
- Antagonists of the RAAS are useful in lowering BP and reducing LVH.
- CCBs such as **diltiazem**, **amlodipine**, **and verapamil** have little utility in the treatment of HFrEF.
- In contrast, each of these drugs has been proposed as being useful in the treatment of HFpEF.

Individual Agents used in management of heart failure

Diuretics

- Recommended in all patients with clinical evidence of fluid retention.
- Do not alter disease progression or prolong survival
- Loop diuretics are used frequently in HF.
- Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function.
- Combination of loop plus a thiazide or thiazide like diuretic (metolazone); also combine with aldosterone antagonist.
- If patient has refractory edema then may have impaired oral diuretic absorption so thus requiring IV therapy.
- Thiazides may be preferred only;
  - Mild fluid retention and
  - Elevated blood pressure

Loop Diuretics

	Furosemide	Bumetanide	Torsemide
Usual daily dose (oral)	20–160 mg	0.5–4 mg	10–80 mg
Ceiling dose:			
Normal renal function	80–160 mg	1–2 mg	20–40 mg
CrCL 20–50 mL/minute	160 mg	2 mg	40 mg
CrCL less than 20 mL/minute	400 mg	8–10 mg	100 mg
Bioavailability	10–100% (average 50%)	80–90%	80–100%
Affected by food	Yes	Yes	No
Half-life	0.3–3.4 hours	0.3–1.5 hours	3–4 hours

CrCL, creatinine clearance.

ACEIs

- ACEIs decrease angiotensin II and aldosterone, attenuating many of their deleterious effects, including:
  - Reducing ventricular remodeling
  - Myocardial fibrosis
  - Myocyte apoptosis
  - Cardiac hypertrophy
  - Norepinephrine release
  - Vasoconstriction
  - Sodium and water retention.

Cont…

- Improve symptoms, slow disease progression and decrease mortality in patients with HF and reduced LVEF (stage C).
- These patients should receive ACE inhibitors unless contraindications are present.
- ACEIs should also be used to prevent the development of HF in at-risk patients (i.e., stages A and B).

Dosing and Monitoring for Neurohormonal Blocking Agents

Drug	Initial Daily Dose	Target or Maximum Daily Dose	Monitoring
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	BP
Enalapril	2.5 mg twice	10–20 mg twice	Electrolytes (K^+, BUN, SCr) at baseline, 2 weeks, and after dose titration, CBC periodically
Fosinopril	5–10 mg once	40 mg once	
Lisinopril	2.5–5 mg once	20–40 mg once	
Perindopril	2 mg once	8–16 mg once	
Quinopril	5 mg once	20 mg twice	Adverse effects: cough, angioedema
Ramipril	1.25–2.5 mg once	10 mg once	
Trandolapril	1 mg once	4 mg once	
Angiotensin Receptor Blockers			
Candesartan	4–8 mg once	32 mg once	BP
Losartan	25–50 mg once	50–100 mg once	Electrolytes (K^+, BUN, SCr) at baseline, 2 weeks, and after dose titration, CBC periodically
Valsartan	20–40 mg once	160 mg twice	Adverse effects: cough, angioedema

ARBs

- If a patient is unable to tolerate ACEIs because of cough then ARBs maybe an option
- ARBs are generally more expensive then ACEIs
- ARBs many be considered as alternative therapy for patients who have developed angioedema while taking ACEIs but there are some cases of which patients also had angioedema while taking ARBs. Thus, extreme caution is needed.
- ARBs are also used as an additional therapy in patients who have symptoms that persist (i.e. patients who remain NYHA class II, III, or IV despite receiving an optimal dose of an ACEI and a beta blocker.

Beta Blockers

- Long term treatment with beta blockers can lessen the symptoms of HF, improve clinical status of patients and enhance the patient's overall well being.
- Also, can reduce risk of death and hospitalization
- Stage C HF should be treated with beta blockers
- Should be initiated as soon as LV dysfunction is diagnosed
  - Initiate with very low doses then gradually increase as tolerated
- MOA: Bisoprolol and Metoprolol succinate both selectively block beta 1 receptors. Carvedilol block alpha 1, beta 1 and beta 2 receptors.
- **SE:** fatigue, dizziness, bradycardia, bronchospasm, hypoglycemia, arrhythmia, worsening HF, hypotension.
- **CI:** advanced heart block or symptomatic bradycardia

	Dose	Frequency	Half-life(h)	Comment
Carvedilol	Target: 25–50 mg Start:3.125 mg	Twice daily	6-10	May initially exacerbate symptoms but if initiated at low dose and slowly titrated can improve long-term survival, even in elderly patients with heart failure
Bisoprolol	Target: 10 mg Start: 1.25mg	Once daily	10-12	
Metoprolol(succinate) CR/XL	Target: 200mg Start: 12.5-25mg	Once daily	3-7	

- BP, HR, ECG, signs and symptoms of worsening HF, blood glucose
- Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms.

Aldosterone Antagonists

- **Spironolactone** and **eplerenone** block the mineralocorticoid receptor, the target site for aldosterone.
  - In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion.
  - However, diuretic effects are minimal, suggesting that their therapeutic benefits result from other actions.
  - Effects in the heart attenuate cardiac fibrosis and ventricular remodeling.

Cont…

- Based on clinical trial results demonstrating reduced mortality, low-dose aldosterone antagonists may be appropriate for:
  - Patients with moderately severe to severe HF who are receiving standard therapy and
  - Those with LV dysfunction early after MI.
- Initial doses should be low especially in the elderly and those with diabetes or creatinine clearance <50 mL/min.
  - Spironolactone 12.5 mg/day up to 25 mg daily
  - Eplerenone 25 mg/day target 50mg once daily
- Risks of serious **hyperkalemia** and **worsening renal function**

Cont…

- Thus, aldosterone antagonists must be used cautiously and with careful monitoring of renal function and potassium concentration.
- They **should be avoided** in patients with:
  - Renal impairment Crcr<30 mL/min
  - Recent worsening of renal function
  - High-normal potassium levels >5.0 mEq/L or
  - A history of severe hyperkalemia.

  - Decrease or discontinue potassium supplements
  - Avoid triple therapy with an ACE inhibitor, ARB, and aldosterone antagonist
  - Avoid concomitant use of NSAIDs or COX-2 inhibitors.
  - Avoid concomitant use of high-dose ACE inhibitors or ARBs.

Hydralazine 37.5mg and Isosorbide dinitrate 20mg (BIDIL)

- Can be used for patients with more severe symptoms and ACEIs intolerance
- African Americans respond better to this combination with reduced rate of hospitalization, improved quality of life and increased survival
  - When used in addition to standard therapy
- MOA: Hydralazine relaxes arterial smooth muscle; isosorbide dinitrate vasodilate arteries and veins. It releases nitric oxide leading to relaxed vascular smooth muscle
- SE: headache, dizziness, nausea, hypotension. Malaise, cholecystitis
- Dose:
  - Start- 1 tablet 3x a day
  - Max- 2 tablets 3x a day

Digoxin

- Although digoxin has positive inotropic effects
- It has neurohormonal effects.

- Attenuates the excessive sympathetic nervous system activation present in HF patients, perhaps by reducing central sympathetic outflow and improving impaired baroreceptor function.
- It also increases parasympathetic activity in HF patients and decreases heart rate, thus enhancing diastolic filling.
- Digoxin does not improve survival in patients with HF but does provide symptomatic benefits.
- Digoxin's level of recommendation for treatment in HF has been lowered.

Cont…

- In patients with HF and supraventricular tachyarrhythmias such as atrial fibrillation, digoxin should be considered early in therapy to help control ventricular response rate.
- For patients in normal sinus rhythm, effects on symptom reduction and quality of life improvement are evident in patients with mild to severe HF.
- Therefore, it should be used together with standard HF therapies (ACEIs, β-blockers, and diuretics) in patients with symptomatic HF to reduce hospitalizations.

Cont…

- Doses should be adjusted to achieve plasma digoxin concentration of 0.5 to 1 ng/mL.
- Higher plasma levels are not associated with additional benefits but may increase the risk of toxicity.
- Most patients with normal renal function can achieve this level with a dose of 0.125 mg/day.
- Patients with decreased renal function, the elderly, or those receiving interacting drugs (e.g., amiodarone)
  - Should receive 0.125 mg every other day

Cont…

- In the absence of supraventricular tachyarrhythmias,
  - a loading dose is not indicated because digoxin is a mild inotropic agent that produces gradual effects over several hours, even after loading.
- Blood samples for measuring plasma digoxin concentrations should be collected at least 6 hours, and preferably 12 hours or more, after the last dose.

Clinical Pharmacokinetics of Digoxin

Oral bioavailability	
Tablets	0.5–0.9 (0.65)[a]
Elixir	0.75–0.85 (0.80)
Capsules	0.9–1.0 (0.95)
Onset of action	
Oral	1.5–6 h
Intravenous	15–30 min
Peak effect	
Oral	4–6 h
Intravenous	1.5–4 h
Terminal half-life	
Normal renal function	36 h
Anuric patients	5 days
Volume of distribution at steady state	7.3 L/kg
Fraction unbound in plasma	0.75–0.80
Fraction excreted unchanged in urine	0.65–0.70

Evaluation Of Therapeutic Outcomes
Chronic Heart Failure

- Patients should be asked about the presence and severity of symptoms and how the symptoms affect their daily activities.
- The efficacy of **diuretic** treatment is evaluated by disappearance of the signs and symptoms of excess fluid retention.
- Physical examination should focus on:
  - Body weight
  - Extent of jugular venous distension
  - Presence of hepatojugular reflux
  - Presence and severity of pulmonary congestion
    - Rales, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea
  - Presence and severity of peripheral edema.

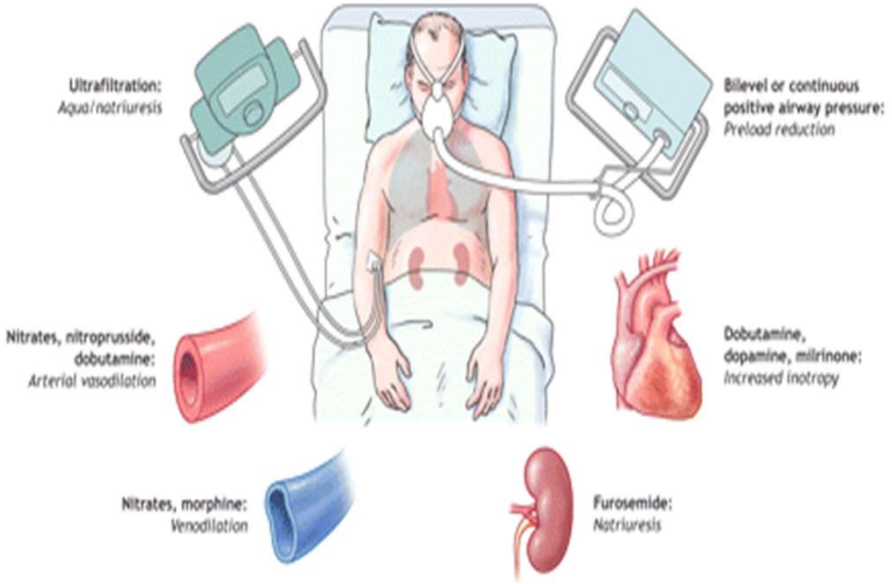
Cont…

- Other outcomes include improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in heart rate.
- Blood pressure should be monitored to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- **Body weight** is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes to their healthcare provider so that adjustments can be made in diuretic doses.

Cont…

- Symptoms may worsen initially on β-blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes and renal function is mandatory in patients with HF.

Acute Decompensated CHF



Acute Decompensated CHF

- The initial goal is to stabilize the patient's condition with conservative measures that improve patient comfort, avoid mechanical ventilatory support, limit cardiac ischemia and attenuate the need for hospital admission.
- IV Loop diuretics for volume overload patients {PCWP & BUN-monitoring}.
- Long-term digoxin therapy should not be stopped during acute decompensated heart failure-may worsen cardiac function.

Acute Decompensated CHF

- Peripheral ultrafiltration may be the most promising new treatment option for patients with acute decompensated heart failure
- In patients with pulmonary edema and hypoxia, the use of supplemental oxygen is recommended.
- Short-term positive pressure ventilation should be considered first-line treatment of acute cardiogenic pulmonary edema.

Acute Decompensated CHF

- Milrinone, dobutamine and dopamine continue to be used relatively frequently in the management of acute decompensated heart failure, especially when more conservative therapies fail.
- β-agonists and phoshodiesterase inhibitors should typically be avoided or limited to short-term or palliative use.

Hospitalized Patients

- Dopamine
- Dobutamine
- Inamrinone
- Milrinone
- Nesiritide

- Combinations have also been studied with better outcomes due to different MOA.

More aggressive therapies

- Ventricular support (intra-aortic balloon counterpulsation or left-ventricular assist device)
- Dialysis
- Heart transplantation — versus hospice

Non Pharmacological Treatment

- Life style and exercise
  - Restrict sodium intake to < 2gms a day
  - Structured aerobic exercise, improved quality of life in patients with heart failure
    - Also may reduce risk of death and hospitalization
- Implantable Cardioverter Defibrillators
  - Reduces risk of sudden death in patients with left ventricular systolic dysfunction
  - Indicated for secondary prevention in patients who survived an unprovoked episodes of ventricular fibrillation or sustained ventricular tachycardia
- Cardiac Resynchronization therapy
  - Recommended for patients with severe symptoms (NYHA class III or IV, an ejection fraction that is persistently < 35%, sinus rhythm and a QRS duration of 120msec or more.
- Transplant Surgery
- Organizations/support groups

Evaluation Of Therapeutic Outcomes
Acute Decompensated Heart Failure

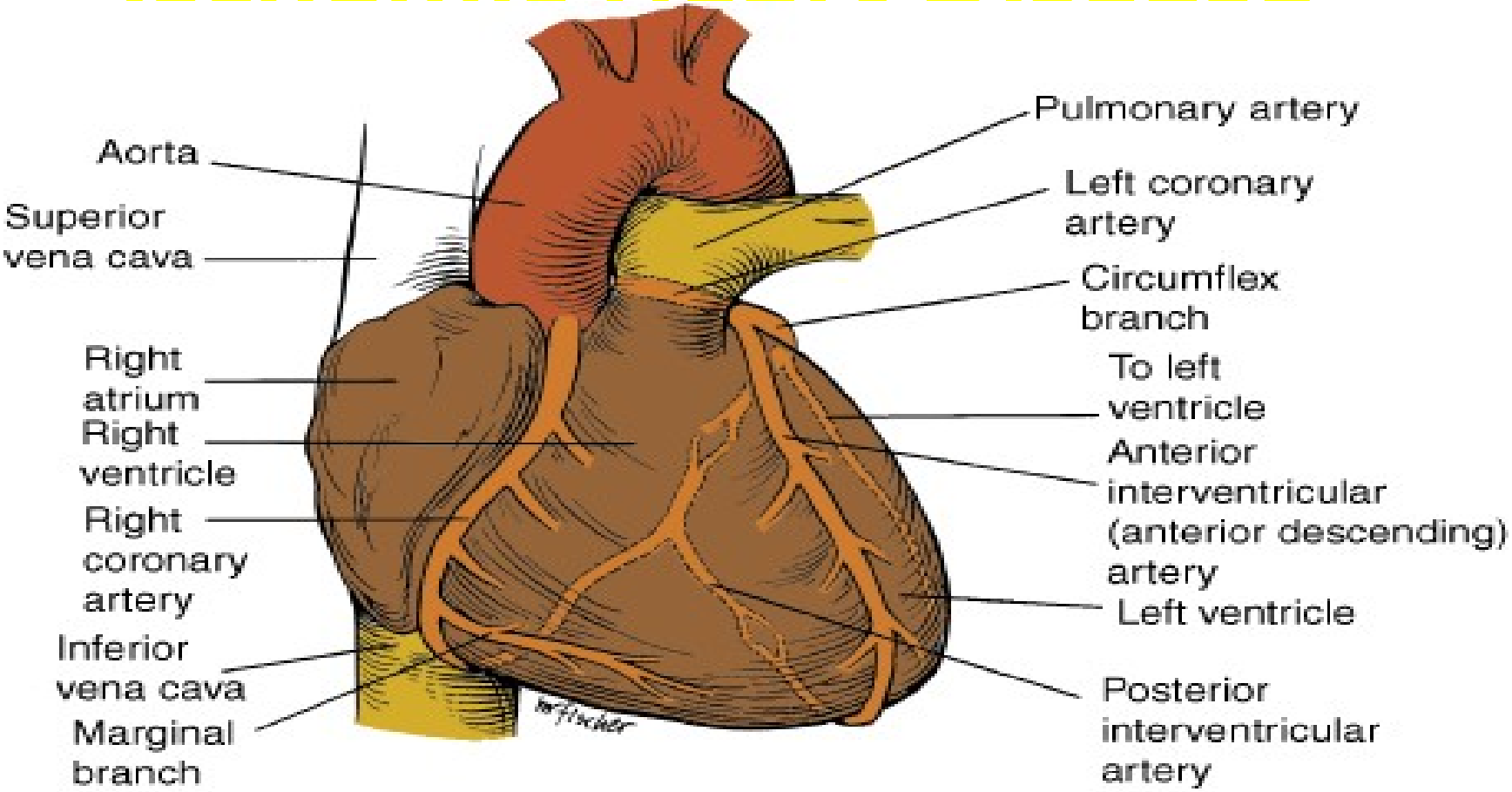
- Initial stabilization requires achievement of adequate arterial oxygen saturation and content.
- Cardiac index and blood pressure must be sufficient to ensure adequate organ perfusion, as assessed by:
  - Alert mental status
  - Creatinine clearance sufficient to prevent metabolic azotemic complications
  - Hepatic function adequate to maintain synthetic and excretory functions

Cont…

- A stable heart rate and rhythm
- Absence of ongoing myocardial ischemia or infarction
- Skeletal muscle and skin blood flow sufficient to prevent ischemic injury and
- Normal arterial pH (7.34 to 7.47) with a normal serum lactate concentration.

- Discharge from the intensive care unit requires maintenance of the preceding parameters in the absence of;
  - Ongoing IV infusion therapy
  - Mechanical circulatory support or positive-pressure

Ischemic Heart Disease



DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

Learning Objectives

- Differentiate between the pathophysiology of chronic stable angina and acute coronary syndromes
- Identify risk factors
- Recognize the symptoms and diagnostic criteria
- Identify the treatment goals and appropriate lifestyle modifications and pharmacologic therapy
- Design an appropriate therapeutic regimen
- Formulate a monitoring plan to assess effectiveness and adverse effects of drug regimen

Introduction (1)

- The term “ischemic” refers to a decreased supply of oxygenated blood.
- Ischemic heart disease (IHD) is defined as a lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction.
- Ischemic heart disease results from an imbalance between myocardial oxygen supply and oxygen demand.

Introduction (2)

- **IHD classification**
  - Chronic Stable angina /exertional angina/
    - Have a reproducible pattern of angina that is associated with a certain level of physical activity
  - Acute coronary syndrome
    - Unstable angina
      - Experience new-onset angina or a change in their angina intensity, frequency, or duration
    - non ST elevation MI
    - ST elevation MI

Determinants Of Cardiac Oxygen Demand And Oxygen Supply

- The principal determinants of cardiac oxygen demand are:
  - Heart rate
  - Myocardial contractility
  - Intramyocardial wall tension
    - Which is determined by: cardiac preload and cardiac afterload.
- Cardiac oxygen supply is determined by myocardial blood flow.

Determinants Of Cardiac Oxygen Demand And Oxygen Supply

↑ Demand may be due to:

- ↑HR
- ↑ Ventricle wall tension (as in hypertension)
- ↑ ventricular contractility

Decreased O_2 supply:

Decreased blood coronary flow due to:

-Fixed atherosclerotic narrowing

-Coronary spasm

-Non occlusive thrombus

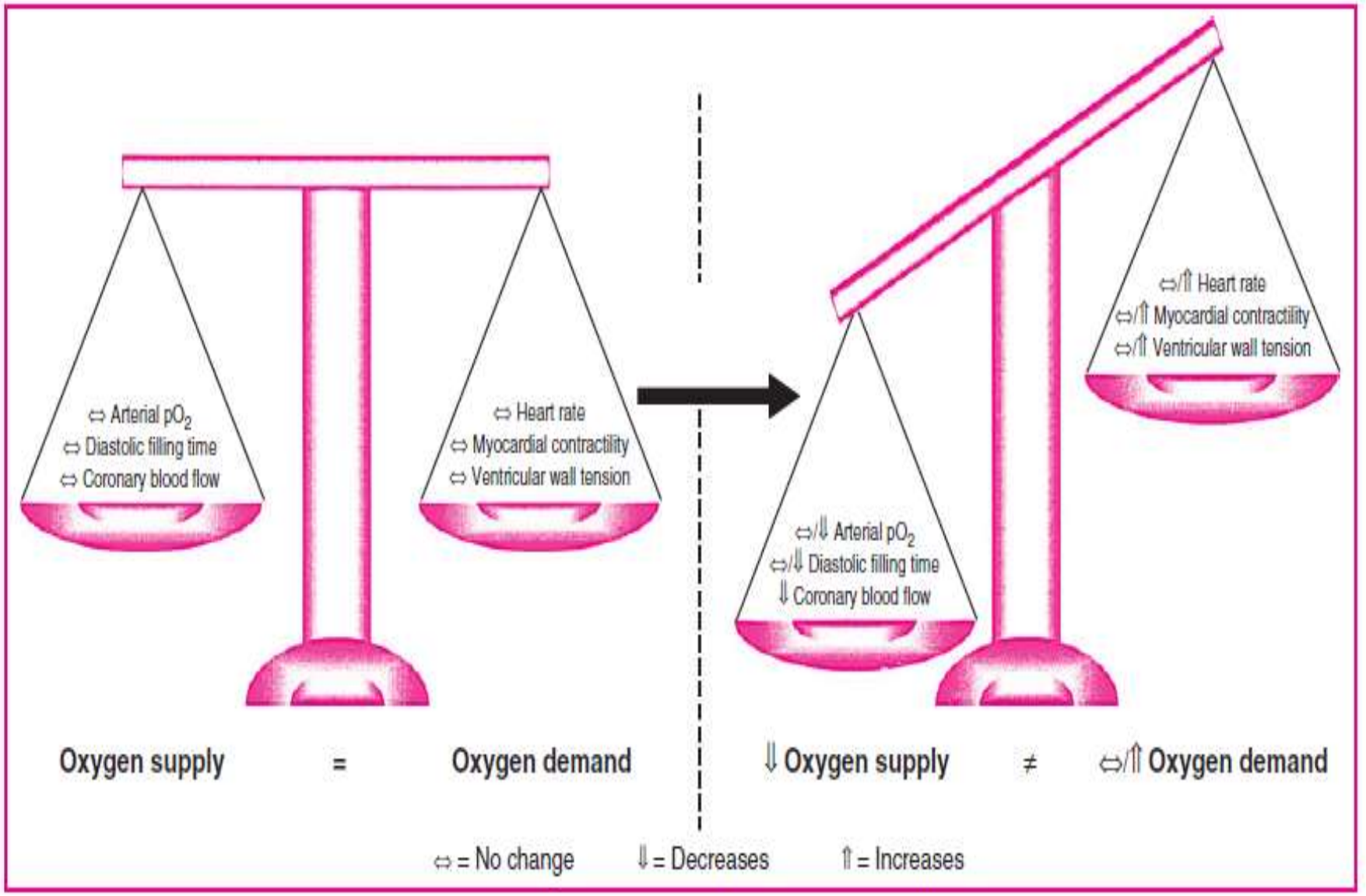


Fig I: The balance between myocardial oxygen supply and demand and the various factors that affect each.

Risk factors for IHD

- **Unalterable**
  - Gender
  - Age (male ≥ 45 year, female ≥ 55 years)
  - Family history or genetic composition
  - Environmental influences such as climate, air pollution, trace metal composition of drinking water

Risk factors for IHD

- **Alterable**
  - Smoking
  - Hypertension
  - Diabetes mellitus
  - Dyslipidemia
  - Obesity
  - Sedentary lifestyle
  - Psychosocial factors such as stress and type A behavior patterns

Stable angina pectoris- pathophysiology

- Stable angina is triggered most often by an increase in physical activity.
  - Emotional excitement, large meals, and cold exposure may also precipitate an attack.
- The underlying cause of exertional angina is coronary artery disease (CAD), a condition characterized by deposition of fatty plaque in the arterial wall.
- In both the healthy heart and the heart with CAD, oxygen supply and oxygen demand are in balance during rest.

Stable angina pectoris- Pathophysiology

- In the healthy heart, as cardiac oxygen demand rises, coronary arterioles dilate, causing blood flow to increase.
  - The increase keeps oxygen supply in balance with oxygen demand.
- By contrast, in people with CAD, arterioles in the affected region are already fully dilated during rest.
  - Hence, when exertion occurs, there is no way to increase blood flow to compensate for the increase in oxygen demand.

Stable angina pectoris- Pathophysiology

- The resultant imbalance between oxygen supply and oxygen demand causes anginal pain.

- Over time, an established plaque may become unstable and rupture, leading to an ACS.

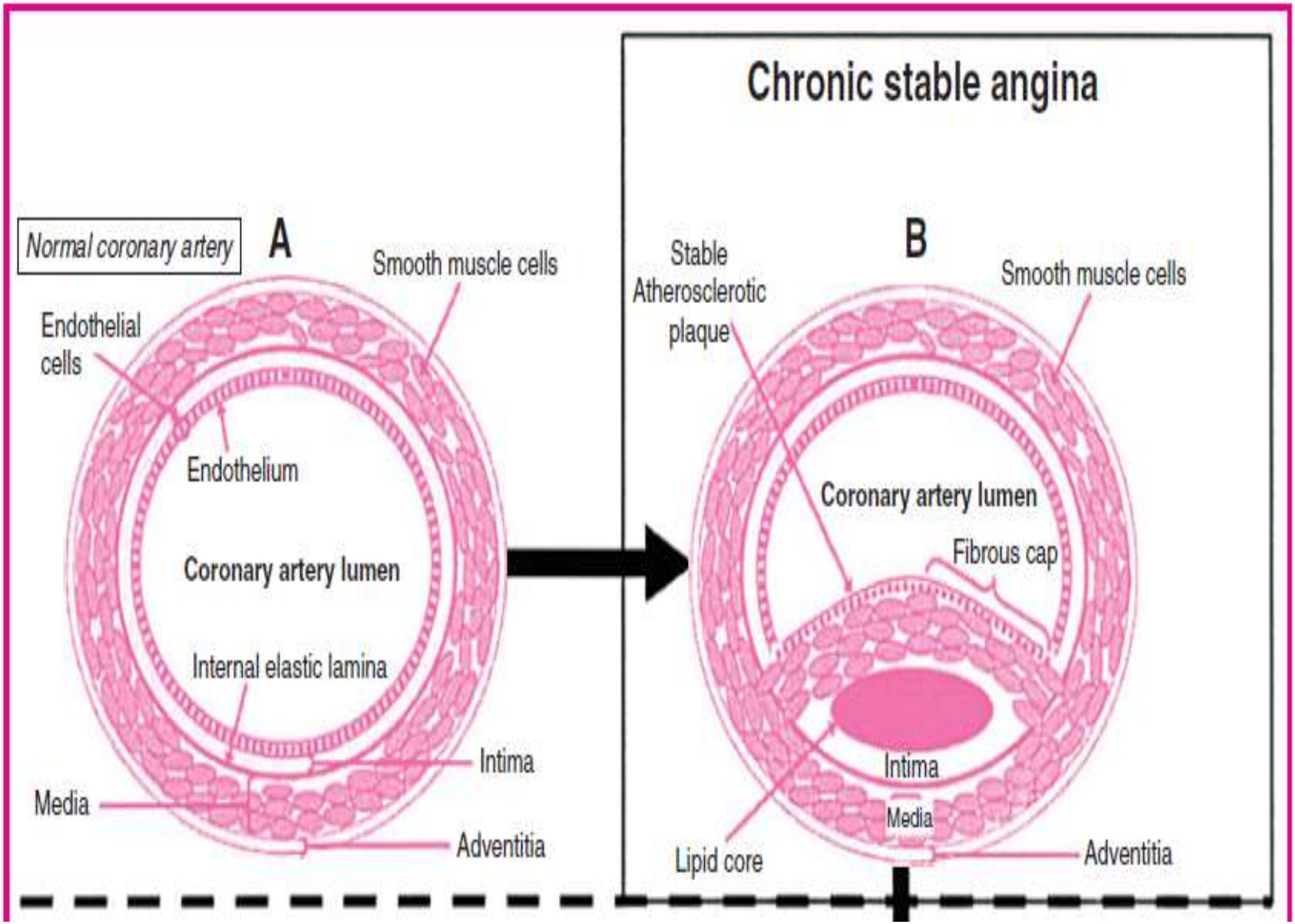


Fig 2: Pathophysiology of chronic stable angina

Clinical Presentation

- **General**
  - Patients often have a reproducible pattern of pain or other symptoms that appear after a specific amount of exertion.
  - Increased frequency, severity, duration, or symptoms at rest suggest an unstable angina pattern, and the patient should seek help immediately.

Clinical Presentation

- **Symptoms**
  - Sensation of pressure or burning over the sternum or near it, often but not always radiating to the left jaw, shoulder, and arm; also chest tightness and shortness of breath.
  - Pain usually lasts from 0.5 to 30 minutes often with a visceral quality (deep location).
  - Precipitating factors include exercise, cold environment, walking after a meal, emotional upset, fright, anger, and coitus.
  - Relief occurs with rest and nitroglycerin.

Differential Diagnosis of Episodic Chest Pain Resembling Angina Pectoris

	Duration	Quality	Provocation	Relief	Location	Comment
Effort angina	5 – 15 min	Visceral (pressure)	During effort or emotion	Rest, NTG	Substernal, radiates	First episode vivid
Rest angina	5 – 15 min	Visceral (pressure)	Spontaneous (? with exercise)	NTG	Substernal, radiates	Often nocturnal
Mitral prolapse	Min – hours	Superficial (rarely visceral)	Spontaneous (no pattern)	Time	Left anterior	No pattern, variable
Esophageal reflux	10 min – 1 h	Visceral	Spontaneous, cold liquids, exercise, lying down	Foods, antacids, H2 blockers, proton pump inhibitors, NTG	Substernal, radiates	Mimics angina
Peptic ulcer	Hours	Visceral, burning	Lack of food, "acid" foods	Foods, antacids, H_2 blockers, proton pump inhibitors	Epigastric, substernal	

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy: A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com

Differential Diagnosis of Episodic Chest Pain Resembling Angina Pectoris

	Duration	Quality	Provocation	Relief	Location	Comment
Biliary disease	Hours	Visceral (wax and wane)	Spontaneous, food	Time, analgesia	Epigastric, radiates	Colic
Cervical disk	Variable (gradually subsides)	Superficial	Head and neck, movement and palpation	Time, analgesia	Arm, neck	Not relieved by rest
Hyperventilation	2 – 3 min	Visceral	Emotion, tachypnea	Stimulus removed	Substernal	Facial paraesthesia
Musculoskeletal	Variable	Superficial	Movement, palpation	Time, analgesia	Multiple	Tenderness
Pulmonary	30 min	Visceral (pressure)	Often spontaneous	Rest, time broncho-dilator	Substernal	Dyspneic

Clinical Presentation

- **Signs**
  - Abnormal precordial (over the heart) systolic bulge
  - Abnormal heart sounds

Clinical Presentation

- **Laboratory Tests**
  - Lipid panel (LDL, HDL, TG, total Cholesterol)
  - RBS/FBS
  - Blood pressure (BP)
  - C-reactive protein
  - Renal function test
  - CBC
  - CXR
  - Serum troponin or creatine kinase
  - ECG

Treatment

- **Goals of therapy**
  - Prevent acute coronary syndromes and death
  - Alleviate acute symptoms of myocardial ischemia
  - Prevent recurrent symptoms of myocardial ischemia
  - Avoid or minimize adverse treatment effects.

Treatment

- **General Approach to Treatment**
- The primary strategies for preventing ACS and death are to:
  - Modify cardiovascular risk factors
  - Slow the progression of coronary atherosclerosis
  - Stabilize existing atherosclerotic plaques

Treatment

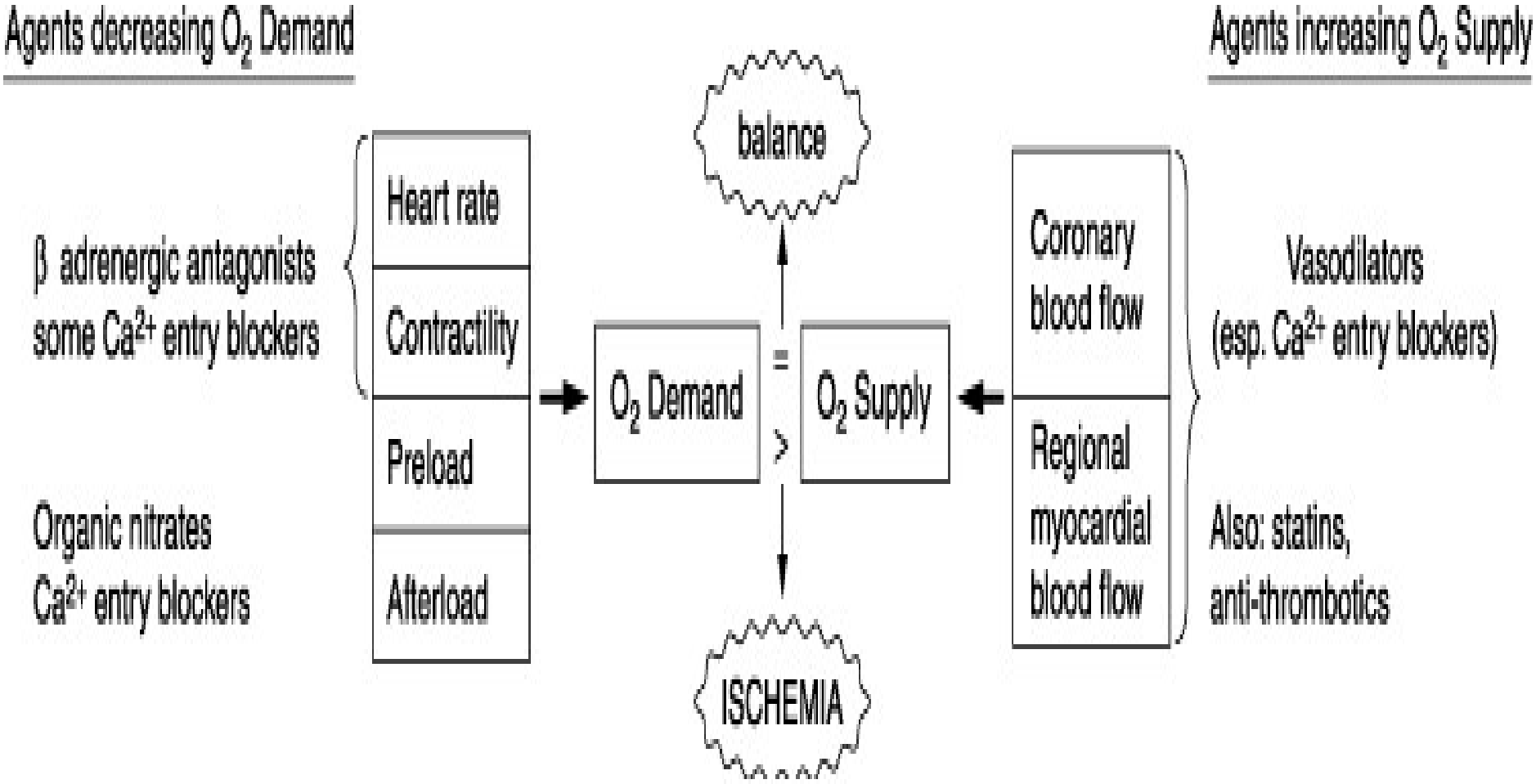
- **Risk Factor Modification**
  - Primary prevention of IHD through the identification and modification of risk factors prior to the initial morbid event would be the optimal management

Treatment

- Non-pharmacologic
- **Percutaneous coronary intervention** involves the threading of a catheter to the site of an atherosclerotic lesion in a coronary artery.
  - A balloon on the tip of the catheter is inflated to compress the plaque against the arterial wall (balloon angioplasty) or a device is used to cut away the plaque.
  - Often, a stent (a wire mesh tube resembling a spring) is placed at the site of balloon angioplasty to hold the vessel open.
- **Coronary artery bypass graft surgery** involves using a leg vein or mammary artery to form a conduit around an atherosclerotic plaque.

Treatment

- **Drug therapy**
  - β-blockers
  - Nitrates
  - Calcium channel blockers



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

β-Adrenergic Blocking Agents

- The predominant receptor type in the heart is the β_1-receptor, and competitive blockade minimizes the influence of endogenous catecholamines.

- Decreased heart rate, decreased contractility, and a slight to moderate decrease in blood pressure with -adrenergic receptor antagonism reduce MVO_2.

- β-Blockers do not improve myocardial oxygen supply.

β-Adrenergic Blocking Agents

- Ideal candidates for β-blockers include:
  - Patients in whom physical activity is a prominent cause of attacks
  - those with coexisting hypertension, supraventricular arrhythmias, or postmyocardial infarction angina
  - those with anxiety associated with anginal episodes

β-Adrenergic Blocking Agents

- β-adrenoreceptor blockade is effective in chronic exertional angina as monotherapy and in combination with nitrates and/or calcium channel antagonists.
- β-blockers should be the first-line drug in chronic angina requiring daily maintenance therapy because β-blockers are more effective in:
  - reducing episodes of silent ischemia
  - reducing early morning peak of ischemic activity
  - improving mortality after Q-wave MI than nitrates or calcium channel blockers

β-Adrenergic Blocking Agents

- If β-blockers are ineffective or not tolerated, then monotherapy with a calcium channel blocker may be instituted or, if monotherapy is ineffective for either alone, combination therapy may be instituted.
- Patients with severe angina, rest angina, or variant angina (i.e., a component of coronary artery spasm) may be better treated with calcium channel blockers or long-acting nitrates.

β-Adrenergic Blocking Agents

- Initial doses of β-blockers should be at the lower end of the usual dosing range and titrated to response.

- Treatment objectives include lowering the resting HR to 50 to 60 beats/min and limiting maximal exercise HR to about 100 beats/min or less or 20 beats per minute above the resting heart rate.

- Useful in stable & unstable angina but **contraindicated** in variant or vasospastic angina →↑ spasm.

β-Adrenergic Blocking Agents

- The beneficial effects of β– blockers may be countered to some degree with increased ventricular volume and ejection time.

- β-Blockers with intrinsic sympathomimetic activity
  - produce lesser reductions in myocardial oxygen demand and should be avoided in patients with IHD.

- Other β-blockers appear equally effective at controlling symptoms of angina.

β-Adrenergic Blocking Agents

- β-Blockers are contraindicated in patients with:
  - severe bradycardia (heart rate less than 50 beats per minute)
  - AV conduction defects in the absence of a pacemaker.

- β-Blockers should be used with particular caution in combination with other agents that depress AV conduction (e.g., digoxin, verapamil, and diltiazem) because of increased risk for bradycardia and heart block.

β-Adrenergic Blocking Agents

- contraindications include:
  - Asthma
  - Bronchospastic disease
  - Severe depression
  - Peripheral vascular disease
- β1-Selective blockers are preferred in patients with asthma or chronic obstructive pulmonary disease.

β-Adrenergic Blocking Agents

- All β-blockers may mask the tachycardia and tremor (but not sweating) that commonly accompany episodes of hypoglycemia in diabetes.

- In addition, non-selective β-blockers may alter glucose metabolism and slow recovery from hypoglycemia in insulin dependent diabetes.

- Abrupt β-blocker withdrawal may increase the frequency and severity of angina, possibly because of increased receptor sensitivity to catecholamines after long term β-blockade.

Table 1: Properties and Dosing of β-Blockers in Ischemic Heart Disease

Drug	Receptor affinity	Intrinsic sympathetic activity	Usual dose range
Propranolol	β_1 & β_2	No	20 – 80 mg BID
Timolol	β_1 & β_2	No	10 – 20 mg BID
Nadolol	β_1 & β_2	No	40 – 120 mg QD
Pindolol	β_1 & β_2	Yes	10 – 40 mg BID
Atenolo l	B_1 - selective	No	25 – 100 mg QD
Metoprolol	B_1 - selective	No	50 – 100 mg BID
Bisoprolol	B_1 - selective	No	2.5 – 10 mg QD
Carvedilol	α_1, β_1 & β_2	No	6.25 – 25 mg BID
Labetalol	α_1, β_1 & β_2	Yes at β_2 receptor	100 – 400 mg BID

Nitrates

- Short-acting nitrates are first-line treatment to terminate acute episodes of angina.

- All patients with a history of angina should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms.

Nitrates

- Nitrates
  - ✓primarily cause venodilation
    - ✓reduce preload
  - ✓decrease in ventricular volume and wall tension
    - ✓ reduction in myocardial oxygen demand
  - ✓At higher doses, nitrates may also cause arterial dilation and reduce after load.

Nitrates

- Dilating the epicardial coronary arteries and collateral vessels,
  - ✓ nitrates increase myocardial oxygen supply
  - ✓ Nitrates also relief vasospasm
- At the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually, and repeated every 5 minutes until symptoms resolve.

Nitrates

- Nitrate therapy may be used:
  - to terminate an acute anginal attack
  - to prevent effort- or stress-induced attacks
  - for long-term prophylaxis

Long acting nitrates

- Isosorbide dinitrate, in a sublingual form, has a longer half-life with anti-anginal effects lasting up to 2 hours.
- For patients with more frequent attacks, long-acting nitrates is recommended.
- The major limitation of nitrate therapy is the development of tolerance with continuous use.

Long acting nitrates

- The loss of anti-anginal effects may occur within the first 24 hours of continuous nitrate therapy.
- This event can be because of
  - ✓ depletion of the sulfhydryl groups necessary for the conversion of nitrates to nitric oxide, and
  - ✓ generation of free radicals that degrade nitric oxide.

- Allow a daily nitrate-free interval of at least 8 to 12 hours possibly during the night.

Long acting nitrates

- Monotherapy with nitrates for the prevention of ischemia be avoided for.
  - ❖secondary to nitrate-induced venodilation, reflex increases in sympathetic activity and heart rate, with resultant increases in myocardial oxygen demand.
- ❖Patients are unprotected from ischemia during the nitrate-free interval.

Long acting nitrates

- Treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or calcium channel blocker or a combination of the two.
- β-Blockers attenuate the increase in sympathetic tone and heart rate that occurs during nitrate therapy.
- Inturn, nitrates attenuate the increase in wall tension during β-blocker therapy.

Table 2 :Nitrate Products

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 minutes	5 mcg/min
Sublingual/lingual	1–3	30–60 minutes	0.3 mg
Oral	40	3–6 hours	2.5–9 mg 3 times a day
Ointment	20–60	2–8 hours	0.5–1 in
Patch	40–60	>8 hours	1 patch
Erythritol tetranitrate	5–30	4–6 hours	5–10 mg 3 times a day
Pentaerythritol tetranitrate	30	4–8 hours	10–20 mg 3 times a day
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 hours	2.5–5 mg 3 times a day
Oral	20–40	4–6 hours	5–20 mg 3 times a day
Isosorbide mononitrate	30–60	6–8 hours	20 mg daily, twice a day[a]

Calcium Channel Blockers

- Inhibition of calcium entry into the vascular smooth muscle cells leads to systemic vasodilation and reductions in afterload.
- Inhibition of calcium entry into the cardiac cells leads to reductions in cardiac contractility.
  - Reduction in wall tension
  - Reduction in Cardiac contractility
    - Reduction in myocardial oxygen demand
- The nondihydropyridine CCBs further decrease myocardial oxygen demand.

Calcium Channel Blockers

- Due to their negative **chronotropic effects, verapamil** and diltiazem are generally more effective anti-anginal agents than the dihydropyridine CCBs.
- In addition to decreasing myocardial oxygen demand, CCBs increase myocardial oxygen supply.

Calcium Channel Blockers

- Calcium channel blockers are recommended as initial treatment in IHD when β-blockers are contraindicated or not tolerated.
- In addition, CCBs may be used in combination with β -blockers when initial treatment is unsuccessful.
  - A long-acting dihydropyridine CCB is preferred.
  - Amlodipine and felodipine possess less negative inotropic effects and appear to be safe in patients with left ventricular systolic dysfunction.

Calcium Channel Blockers

- Finally, there is some evidence that short acting calcium channel blockers (particularly short acting nifedipine and nicardipine) may increase the risk of cardiovascular events.

❑ Therefore, short-acting agents should be avoided in the management of IHD

Table 3: Effect of Drug Therapy on Myocardial Oxygen Demand

				LV Wall Tension
		Myocardial	Systolic	
	Heart Rate	Contractility	Pressure	LV Volume
Nitrates	⇑	0	⇓	⇓⇓
β-Blockers	⇓⇓	⇓	⇓	⇑
Nifedipine	⇓	0 or ⇓	0 or ⇓	0 or ⇓
Verapamil	⇓	⇓	⇓	0 or ⇓
Diltiazem	⇓⇓	0 or ⇓	⇓	0 or ⇓

Pharmacotherapy to Prevent Acute Coronary Syndromes and Death

- Anti-platelet agents
- Statins
- ACE inhibitors/ARBs

Antiplatelet Therapy

- Antiplatelet therapy with aspirin should be considered for all patients without contraindications, particularly in patients with a history of myocardial infarction.
- Aspirin doses of 75 to 325 mg daily have been shown to be cardioprotective.
- If aspirin is contraindicated (e.g., aspirin allergy, active peptic ulcer disease, or active internal bleeding) or is not tolerated by the patient, other antiplatelet agents such as clopidogrel should be considered.

Antiplatelet Therapy

- The combination of aspirin and clopidogrel 75 mg daily for up to 9 months was more effective than aspirin alone in decreasing the risk of death, MI, and stroke.

Statins

- Lovastatin, simvastatin, pravastatin, and atorvastatin

✓Potent lipid-lowering agents,

✓Specifically lowering LDL cholesterol

✓Statins should be considered in all patients with IHD at high risk of major adverse cardiac events, regardless of baseline LDL cholesterol

Statins

- Non–lipid-lowering effects
  - – provide additional benefit to patients with IHD
    - Shift LDL cholesterol particle size from predominantly small, dense, highly atherogenic particles to larger, less atherogenic particles.
    - Improve endothelial function leading to more effective vasoactive response of the coronary arteries.
    - Prevent or inhibit inflammation by lowering C-reactive protein and other inflammatory mediators thought to be involved in atherosclerosis.
    - Possibly improving atherosclerotic plaque stability.

ACE inhibitors/ARBs

If no C/I ;ACE inhibitors should be considered in IHD patients with

- ✓ Diabetes mellitus,
- ✓ left ventricular dysfunction,
- ✓ history of MI or
- ✓ Any combination of these

ACE inhibitors/ARBs

- A recent meta-analysis of 22 clinical trials with ACE inhibitors in post-MI patients found that ACE inhibitors reduced 1-year mortality by 16% to 32% percent, and the mortality-reducing effects were sustained for up to 4 years.

Table 4:Doses of ACE inhibitors and Angiotensin Receptor Blockers Indicated in Ischemic Heart Disease (IHD).

Drug	Indications	Usual Dosage in IHD
Angiotensin-Converting Enzyme Inhibitors		
Captopril	HTN, HF, post-MI, diabetic nephropathy	6.25–50 mg 3 times daily
Enalapril	HTN, HF	2.5–40 mg daily in 1–2 divided doses
Fosinopril	HTN, HF	10–80 mg daily in 1–2 divided doses
Lisinopril	HTN, HF, post-MI	2.5–40 mg daily
Perindopril	HTN, IHD	4–8 mg daily
Quinapril	HTN, HF, post-MI	5–20 mg twice daily
Ramipril	HTN, high-risk for IHD, HF, post-MI	2.5–10 mg daily in 1–2 divided doses
Trandolapril	HTN, HF, post-MI	1–4 mg daily
Angiotensin Receptor Blockers		
Candesartan	HTN, HF	4–32 mg daily
Valsartan	HTN, HF, post-MI	80–320 mg daily in 1–2 divided doses

HF, heart failure; HTN, hypertension; MI, myocardial infarction.

Case

- RJ is a 47-year-old man with a history of hypertension who presents to your clinic complaining of chest pain that occurred several times over the past few weeks. RJ describes his chest pain as “a heaviness.” He states that it first occurred while he was mowing the grass. He later felt the same heavy sensation while raking leaves and again while carrying some boxes. The pain was located in the substernal area and radiated to his neck. The pain resolved after about 5 minutes of rest.
- **Are RJ’s symptoms consistent with angina?**
- **What tests would be beneficial in establishing a diagnosis?**
- **What additional objective information do you need in order to create a treatment plan for this patient?**

Acute coronary syndromes

Acute coronary syndromes (ACS)

- Acute coronary syndromes (ACS), including unstable angina (UA) and myocardial infarction (MI), are a form of coronary heart disease (CHD) that comprises the most common cause of CVD death.
- The cause of an acute coronary syndrome is:
  - The rupture of an atherosclerotic plaque
  - Subsequent platelet adherence, activation, and aggregation
  - The activation of the clotting cascade
  - A clot forms composed of fibrin and platelets.

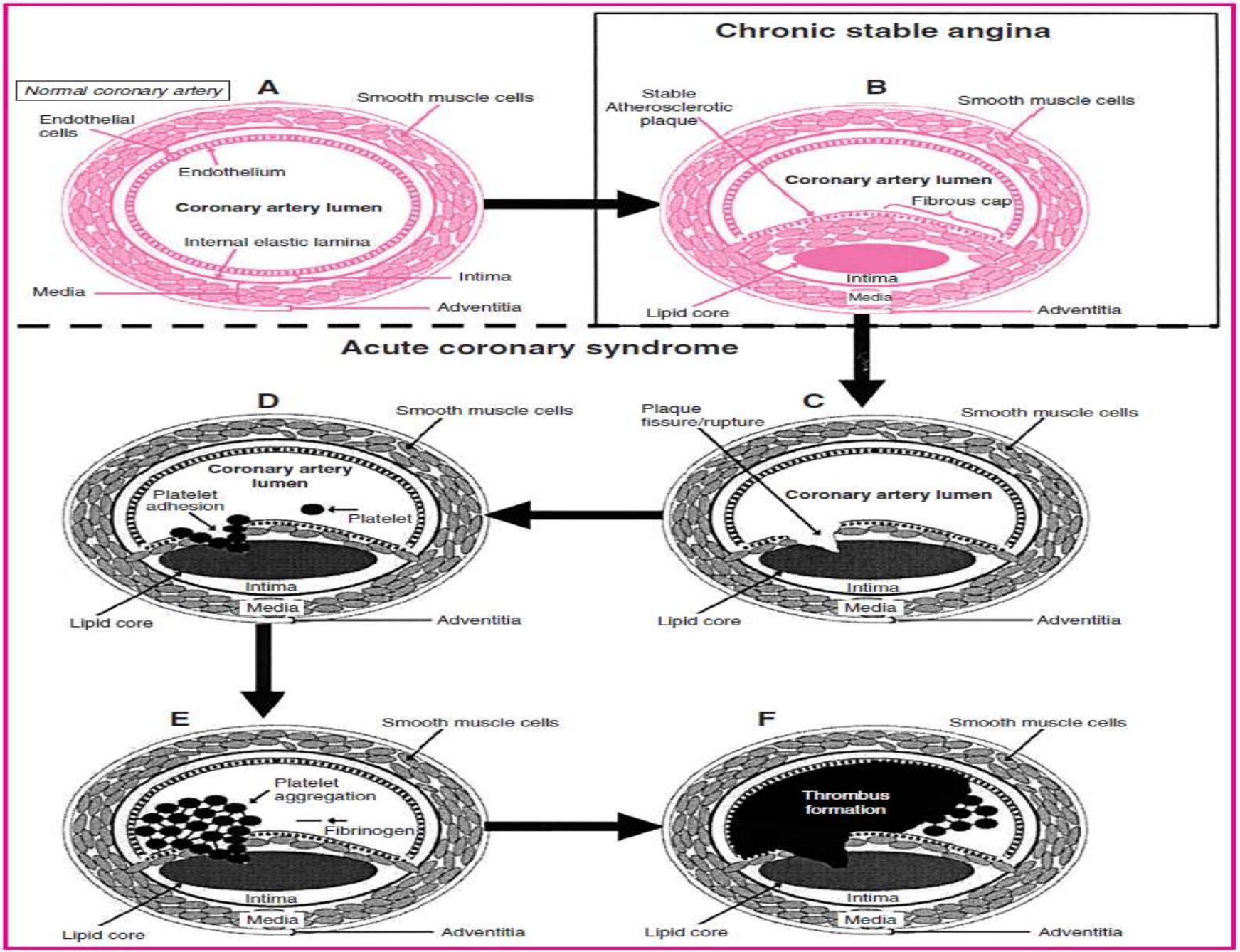


Fig 4: Pathophysiology of chronic stable angina versus ACS

Unstable angina & Non-ST elevation MI

- Unstable angina
  - Angina with at least one of the three features
    - It occurs at rest, lasts > 10 min
    - Severe & of new onset, with in the past 4-6 wks
    - Occurs with a crescendo pattern
- NSTEMI
  - UA + Elevated cardiac biomarkers

ACS - Pathophysiology

- In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus.
- Following plaque rupture, a clot (a partially occlusive or completely occlusive thrombus), forms on top of the ruptured plaque.

ACS - Pathophysiology

- Ventricular remodeling is a process that occurs following an MI.
- It is characterized by left ventricular dilation and reduced pumping function of the left ventricle leading to cardiac failure.
- Heart failure represents one of the principal causes of mortality and morbidity following MI, preventing ventricular remodeling is an important therapeutic goal.

ST-Segment elevation MI

- 30 day mortality rate is 30 %, ½ of it occurs before the patient reaches the hospital
- Pathophysiology
  - Acute plaque rupture→ Platelet adhesion→ Activation of coagulation cascade→ Thrombus formation with total occlusion of arterial lumen.

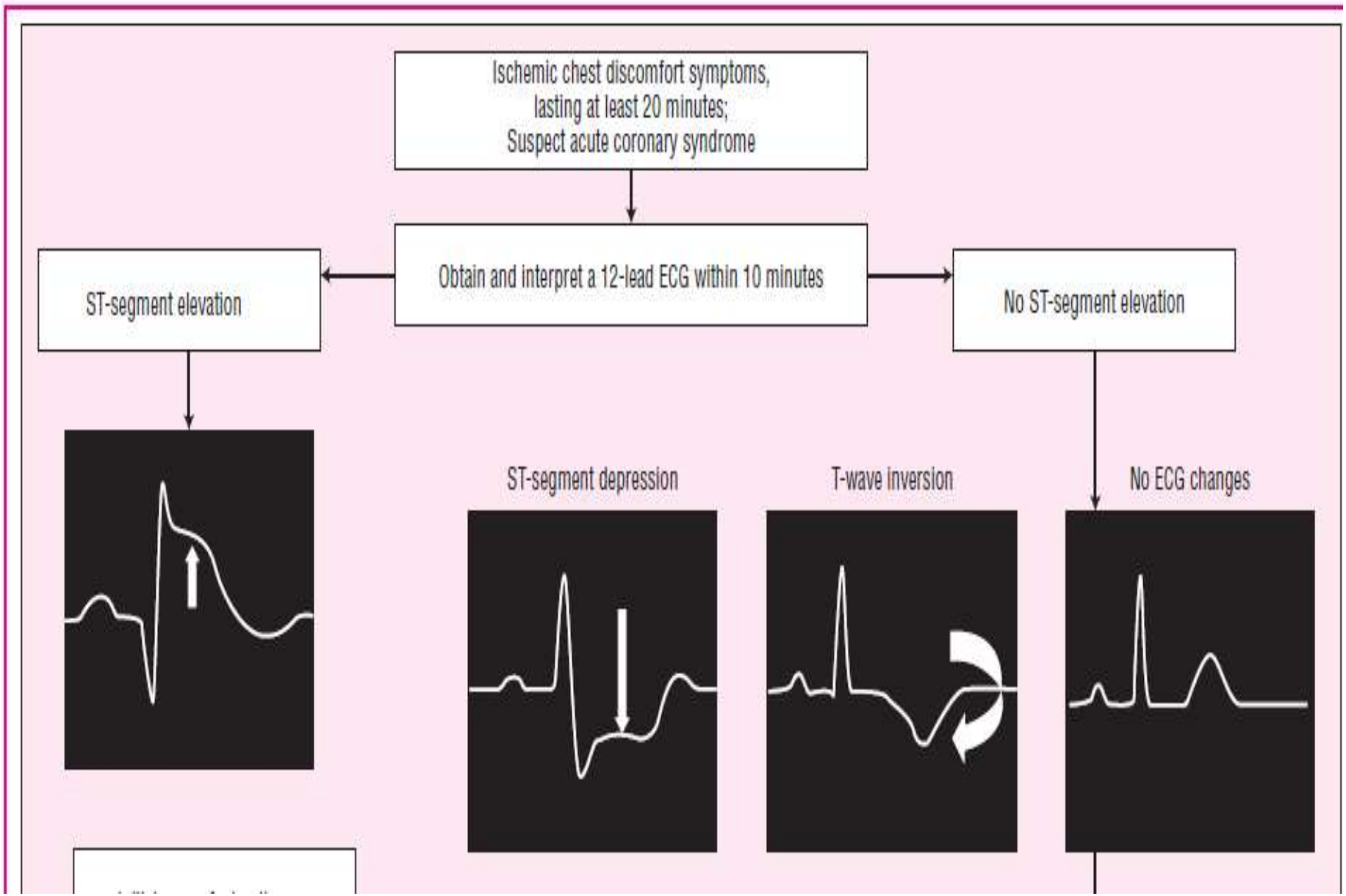


Fig 5: ST-Segment elevation

Clinical Feature

- **Pain**
  - Anginal, severe, prolonged (>30 mins)
- **P/E**
  - Pallor, diaphoresis, anxious patient
  - PR/BP (↑/↓)
  - S3, S4
  - Fever could be present

Lab

- **ECG**
- **Biomarkers**
  - CK-MB: rises with ion 4-8 hrs & returns to normal by 48-72 hrs
  - cTnT & cTnI: rises with in 4-8 hrs but remains elevated for 7-10 days after AMI.
- **Echocardiography**
  - Wall motion abnormality
  - EF estimation
  - Thrombus (LV)
  - RV infarction
  - Pericardial effusion

Biomarkers

- CK-MB- 0 –12 units/L
- cTnI < 0.35 µg/L
- Troponin is specific than CK-MB for myocardial damage, elevated sooner and remains elevated longer than CK-MB.
- cTnI > *2.0 µg/mL* suggests acute myocardial injury.

Treatment

- **Desired Outcomes**
- The short-term goals of treatment for the ACS patient are:
  - Early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA).
  - Prevention of death and other MI complications
  - Prevention of coronary artery reocclusion with reinfarction
  - Relief of ischemic chest discomfort
  - Resolution of ST-segment and T-wave changes on ECG

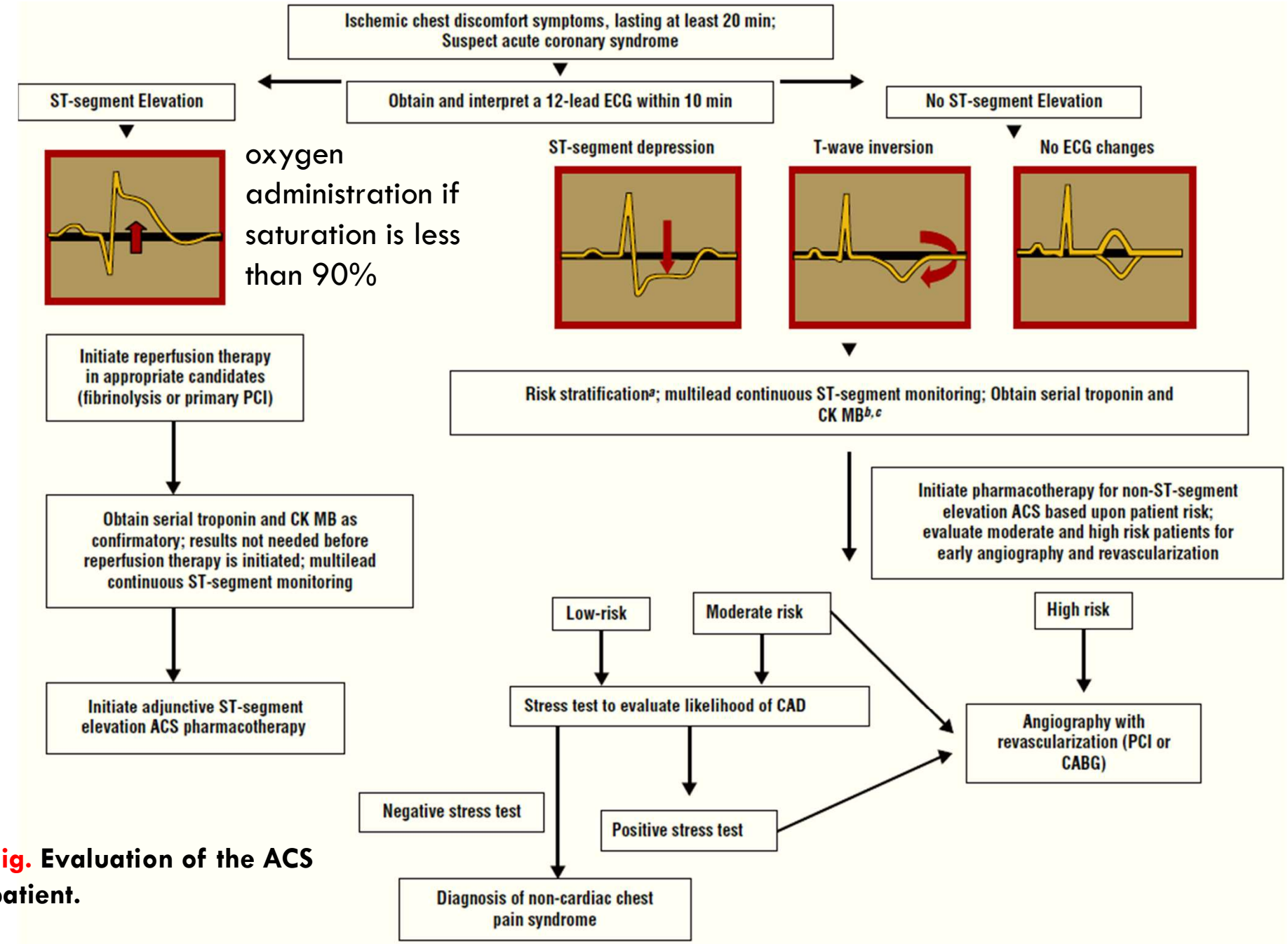


Fig. Evaluation of the ACS patient.

Risk Stratification

- Treat STEMI patients as fast as possible
- NST ACS patients stratified based on clinical presentation, lab findings
  - Risk categories
    - High
    - Medium
    - Low
  - TIMI: Thrombolysis In Myocardial Infarction
- Treatment based on TIMI score

TIMI Risk Score for Non–ST-Segment Elevation Acute Coronary Syndromes

Past Medical History

Age ≥65 years

≥3 Risk factors for CHD

- Hypercholesterolemia
- HTN
- DM
- Smoking
- Family history of premature CHD

Known CAD (50% stenosis of coronary artery)

Use of aspirin within the past 7 days

Clinical Presentation

ST-segment depression (≥0.5 mm)

≥2 episodes of chest discomfort in the past 24 hrs

Positive biochemical marker for infarction[a]

Using the TIMI Risk Score

One point is assigned for each of the seven medical history and clinical presentation findings. The score (point) total is calculated, and the patient is assigned a risk for experiencing the composite end point of death, myocardial infarction or urgent need for revascularization as follows:

High Risk	Medium Risk	Low Risk
TIMI risk score 5–7 points	TIMI risk score 3–4 points	TIMI risk score 0–2 points

[a]Troponin I, troponin T, or creatinine kinase MB greater than the MI detection limit.

- **High-risk** NSTE ACS patients
  - Should undergo early coronary angiography (within 24 to 48 hrs) and revascularization if a significant coronary artery stenosis is found.
- **Moderate-risk patients with positive biochemical markers**
  - Typically undergo angiography and revascularization
- **Moderate-risk patients with negative biochemical markers**
  - May initially undergo a noninvasive stress test

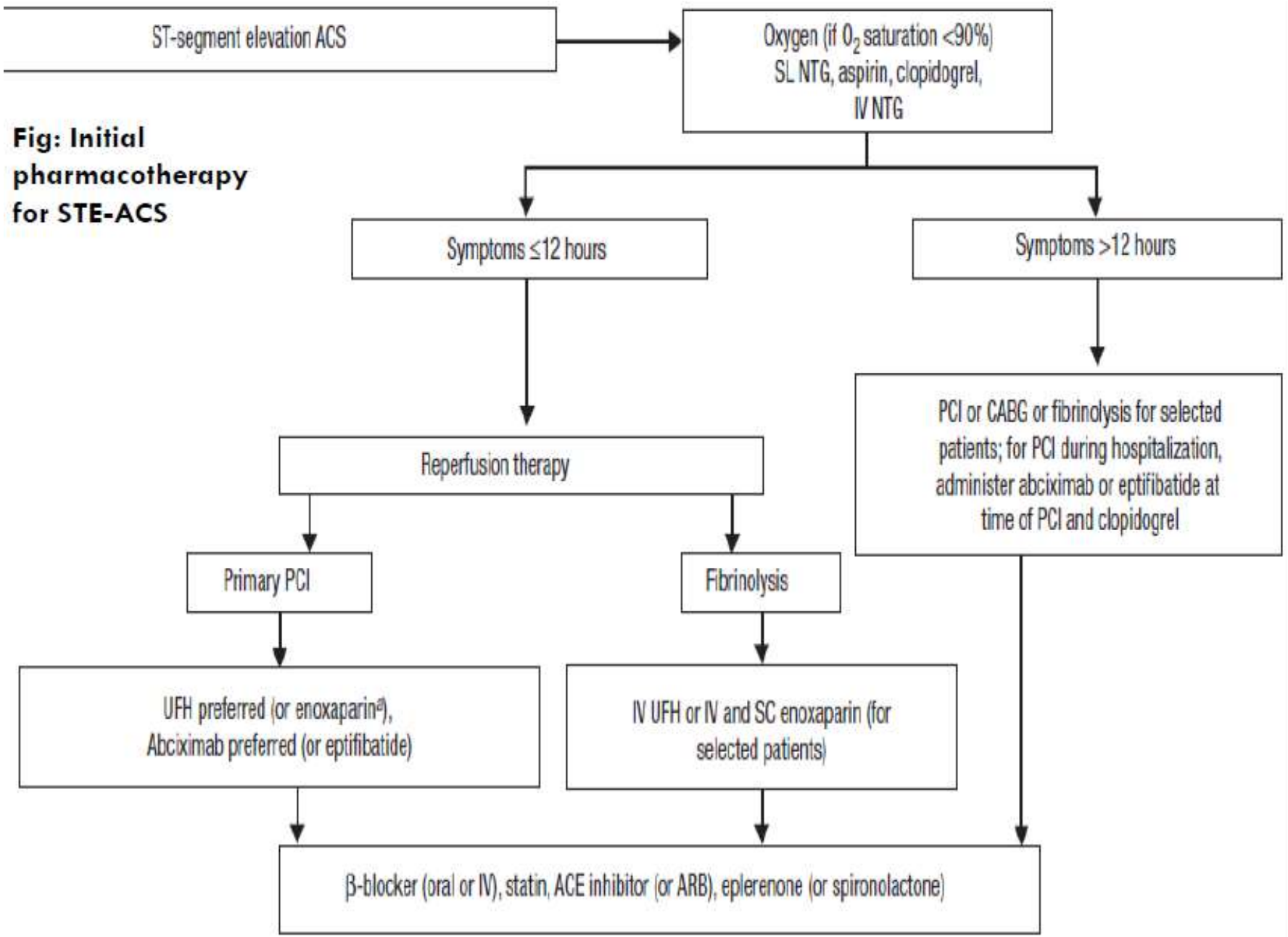
Early Pharmacotherapy For STE ACS

- According to ACC/AHA practice guidelines, early pharmacologic therapy should include:
  - Intranasal oxygen, if SaO_2 <90%
  - Sublingual Nitroglycerin (IV if indicated)
  - Aspirin
  - β-blocker (PO)
  - Anticoagulation
    - UFH, enoxaparin, etc.
  - Morphine can be given for refractory anginal pain
  - Fibrinolysis in ACS only

Early Pharmacotherapy for ST-Segment Elevation ACS

- An ACE inhibitor should be started within 24 hours of presentation, particularly for patients with an LVEF ≤40%, signs of heart failure (HF) or an anterior wall MI, in the absence of contraindications.
- Intravenous (IV) NTG, β-blockers, and an aldosterone antagonist should be administered in select patients.
- A statin should be initiated prior to hospital discharge for patients with an LDL cholesterol of >100 mg/dL.

Fig: Initial pharmacotherapy for STE-ACS



Fibrinolytic Therapy

- Administration of a fibrinolytic agent is indicated in patients with STE ACS who present to the hospital within 12 hours of onset of chest discomfort and have at least 1 mm of STE .

- Fibrinolytic therapy also should be considered in patients presenting within 12–24 hours of onset of chest discomfort and have persistent symptoms of ischemia and at least 1 mm of STE in two or more contiguous leads.

Fibrinolytic Therapy

- The mortality benefit of fibrinolysis is highest with early administration and diminishes after 12 hours.
- Fibrinolytic therapy is preferred over primary PCI in patients who present within 3 hours of symptom onset.
- It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.

Fibrinolytic Therapy

- Include: Alteplase, reteplase, tenecteplase, streptokinase
- Eligible patients should be treated as soon as possible, but preferably within 30 minutes from the time they present to the emergency department, with one of the following regimens:

✓ **Alteplase: 15-mg IV bolus followed by 0.75-mg/kg infusion (maximum** 50 mg) over 30 minutes, followed by 0.5-mg/kg infusion (maximum 35 mg) over 60 minutes (maximum dose 100 mg).

Fibrinolytic Therapy

- **Reteplase**: 10 units IV over 2 minutes, followed 30 minutes later with another 10 units IV over 2 minutes.

- **Tenecteplase:** A single IV bolus dose given over 5 seconds based on patient weight: 30 mg if <60 kg; 35 mg if 60 to 69.9 kg; 40 mg if 70 to 79.9 kg; 45 mg if 80 to 89.9 kg; and 50 mg if 90 kg or greater.

- **Streptokinase: 1.5 million units in 50 mL of normal saline or 5%** dextrose in water IV over 60 minutes.

- **ICH and major bleeding are the most serious side effects.**

Table 5: Indications and Contraindications to Fibrinolytic Therapy According to ACC/AHA Guidelines for Management of Patients with ST-Segment Elevation Myocardial Infarction

Indications

1. Ischemic chest discomfort at least 20 minutes in duration but ≤12 hours since symptom onset
   and
   ST-segment elevation of at least 1 mm in height in ≤2 contiguous leads or
   New or presumed new left bundle-branch block
2. Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset
   and
   ST-segment elevation of at least 1 mm in height in ≥2 contiguous leads

Absolute contraindications

Active internal bleeding (not including menses)
Previous intracranial hemorrhage at any time; ischemic stroke within 3 months
Known intracranial neoplasm
Known structural vascular lesion (e.g., arteriovenous malformation)
Suspected aortic dissection
Significant closed head or facial trauma within 3 months

Table 5: Indications and Contraindications to Fibrinolytic Therapy According to ACC/AHA Guidelines for Management of Patients with ST-Segment Elevation Myocardial Infarction

Relative contraindications

Severe, uncontrolled hypertension on presentation (blood pressure >180/110 mm Hg)

History of prior ischemic stroke >3 months, dementia, or known intracranial pathology not covered above under absolute contraindications

Current use of anticoagulants

Known bleeding diathesis

Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)

Noncompressible vascular puncture (e.g., a recent liver biopsy or carotid artery puncture)

Recent (within 2–4 weeks) internal bleeding

For streptokinase administration, previous streptokinase use (>5 days) or prior allergic reactions

Pregnancy

Active peptic ulcer

History of severe, chronic poorly controlled hypertension

Aspirin

- Early aspirin administration to all patients without contraindications within the first 24 hours of hospital admission is a quality care indicator.

- In patients undergoing PCI, aspirin prevents acute thrombotic occlusion during the procedure.

- In patients experiencing an ACS, an initial dose equal to greater than 160 mg nonenteric aspirin is necessary to achieve rapid platelet inhibition.

Aspirin

- This first dose can be chewed in order to achieve high blood concentrations and rapid platelet inhibition.

- Current data suggest that although an initial dose of 160 to 325 mg is required, long-term therapy with doses of 75 to 150 mg daily are as effective as higher doses and, therefore, a daily maintenance dose of 75 to 160 mg is recommended.

Aspirin

- Although the risk of major bleeding, particularly gastrointestinal bleeding, appears to be reduced by using lower doses of aspirin,
- low-dose aspirin, taken chronically, is not free of adverse effects.
- Patients should be counseled on the potential risk of bleeding.
- Aspirin therapy should be continued indefinitely.

Clopidogrel

- Alternative for patients with ASA allergy
- STE ACS
  - Added to ASA in patients undergoing primary PCI
  - For patients treated with fibrinolytics and in those receiving no revascularization therapy, clopidogrel either 75 mg or 300 mg on day 1 followed by 75 mg once daily should be given for at **least 14 to 28 days in addition to aspirin.**
- NSTE ACS
  - Recommended for most patients in combination with ASA for up to 12 months
- Blocks ADP2Y_{12} receptors on platelets
  - Prevents fibrin binding
- Contraindications:
  - Hypersensitivity, active bleeding , severe bleeding risk
- Adverse effects:
  - Bleeding, nausea, vomiting, diarrhea
- Dosing:
  - 300 to 600 mg PO loading dose
  - followed by 75 mg PO daily
- Duration of therapy depends on type of stent

Glycoprotein IIb/IIIa Receptor Inhibitors

- STE ACS
  - Abciximab indicated for patients undergoing 1 ˚ PCI in combination with ASA, clopidogrel, & UFH
  - Eptifibatide also FDA approved for this indication
- NSTE ACS
  - Tirofiban or eptifibatide recommended for high-risk patients not undergoing revascularization or patients with continued ischemia despite treatment with ASA, clopidogrel & an anticoagulant
  - Abcixicmab or eptifibatide recommended for patients undergoing PCI
- Prevents cross linking of platelets through inhibition of GP IIb/IIIa receptors
- May help with early opening of coronary arteries
- Contraindications:
  - Active bleeding
  - Thrombocytopenia
  - History of stroke
- Adverse effects:
  - Bleeding
  - Immune mediated thrombocytopenia

Anticoagulants

- UFH, administered as an IV bolus followed by a continuous infusion, is a first-line anticoagulant for treatment of patients with STE ACS, both for medical therapy and for patients undergoing PCI.
  - (To prevent reocclusion of an infarct artery)
- Anticoagulant therapy should be initiated in the emergency department and continued for at least 48 hours in selected patients who will be bridged over to receive chronic warfarin anticoagulation following acute MI.

Anticoagulants

- If a patient undergoes PCI, UFH is discontinue immediately after the procedure.

For STEMI, administer 60 units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/h (maximum 1000 units/h)

For NSTE ACS, administer 60–70 units/kg IV bolus (maximum 5000 units) followed by a constant IV infusion at 12–15 units/kg/h (maximum 1000 units/h)

Titrated to maintain an aPTT of 1.5–2.5 times control for NSTE ACS and 50–70 seconds for STEMI

First aPTT should be measured at 4–6 hours for NSTE ACS and STE ACS in patients not treated with fibrinolytics

First aPTT should be measured at 3 hours in patients with STE ACS who are treated with fibrinolytics

Anticoagulants

- The dose of UFH infusion is adjusted frequently to a target activated partial thromboplastin time.

- When coadministered with a fibrinolytic
  - aPTTs above the target range are associated with an increased rate of bleeding,
  - aPTTs below the target range are associated with increased mortality and reinfarction

Anticoagulants

- Limitations of UFH anticoagulation include the need for intravenous infusion therapy, frequent aPTT monitoring, and the risk of heparin-induced thrombocytopenia.

Nitrates

- Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation at higher doses.

- Venodilation lowers preload and myocardial oxygen demand.

- Arterial vasodilation relieves coronary artery vasospasm, dilating coronary arteries to improve myocardial blood flow and oxygenation.

Nitrates

- One SL NTG tablet (0.4 mg) should be administered every 5 minutes for up to three doses to relieve myocardial ischemia.

- If patients have previously been prescribed SL NTG and ischemic chest discomfort persists for more than 5 minutes after the first dose,

  - The patient should be instructed to contact emergency medical services before self-administering subsequent doses in order to activate emergency care sooner.

Nitrates

- Indications for IV therapy include:
  - Persisting ischemic discomfort hypertension, and pulmonary congestion.
  - IV NTG should be continued for approximately 24 hours after ischemia is relieved.

- ACE inhibitors or β-blockers, should not be withheld for nitrates use because the mortality benefit of nitrates is unproven.

Nitrates

- Nitroglycerin should be avoided in
  - Patients with hypotension (systolic pressure below 90 mm Hg)
  - Severe bradycardia (heart rate below 50 bpm)
  - Marked tachycardia (heart rate above 100 bpm)
  - Suspected right ventricular infarction.
  - Men who have taken sildenafil or vardenafil for erectile dysfunction within the last 24 hours, or tadalafil within the last 48 hours.
- Because PCI or CABG restores coronary artery blood flow, NTG is typically not continued following revascularization.

β-Blockers

- A β-blocker should be administered early in the care of patients with STE ACS and continued indefinitely.
- Early administration of a β- blocker within the first 24 hours of hospitalization in patients lacking a contraindication is a quality care indicator.

β-Blockers

- β1- blockade produces a reduction in heart rate, myocardial contractility, and blood pressure, decreasing myocardial oxygen demand.

- The reduction in heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.

- β-blockers reduce the risk for recurrent ischemic, infarct size, risk of reinfarction, and occurrence of ventricular arrhythmias in the hours and days following MI.

β-Blockers

- Initiating IV β-blockers early in the course of STEMI was associated with a lower risk of reinfarction or ventricular fibrillation.
- But, with IV β-blockers there may be an early risk of cardiogenic shock,
  - Especially in patients presenting with pulmonary congestion or systolic blood pressure <120 mm Hg.
- Limit the use of IV β- blockers, to patients:
  - Who are hemodynamically stable
  - Who do not demonstrate any signs or symptoms of decompensated heart failure.

β-Blockers

- Initiation of β-blockers for patients who present with decompensated heart failure can be attempted before hospital discharge in most patients following treatment of acute heart failure,
- β-Blockers are continued indefinitely.

- Because of these effects, β-blockers reduce
  - the risk for recurrent ischemia
  - infarct size
  - risk of re-infarction and
  - occurrence of ventricular arrhythmias.
- The usual doses of β-blockers are as follows

Metoprolol	5 mg by slow IV bolus, repeated every 5 minutes for a total initial dose of 15 mg. This is followed in 15 to 30 minutes by 25 to 50 mg orally every 6 hours.
Propranolol	0.5 to 1 mg slow IV push, followed in 1 to 2 hours by 40 to 80 mg orally every 6 to 8 hours.
Atenolol	5 mg IV dose, followed 5 minutes later by a second 5-mg IV dose; then 50 to 100 mg orally every day beginning 1 to 2 hours after the IV dose.
Esmolol	0.1 mg/kg/min IV, with titration in increments of 0.05 mg/kg/min every 10 to 15 minutes as tolerated by BP

If appropriate, initial IV therapy may be omitted.

Calcium Channel Blockers

- Administration of CCBs in the setting of STE ACS is reserved for patients who have contraindications to β- blockers and is given for relief of ischemic symptoms.

- In patients prescribed CCBs for treatment of hypertension who are not receiving β-blockers and who do not have a contraindication to β-blockers, the CCB should be discontinued and a β-blocker initiated.

Calcium Channel Blockers

- Variant (or Prinzmetal) angina caused by coronary vasospasm
  - Calcium channel blockers and/or NTG generally are considered the agents of choice in these patients because they can reverse coronary spasm by inducing smooth muscle relaxation in the coronary arteries.
  - β-blockers generally should be avoided in these patients unless they have uncontrolled sinus tachycardia (>100 beats/min).

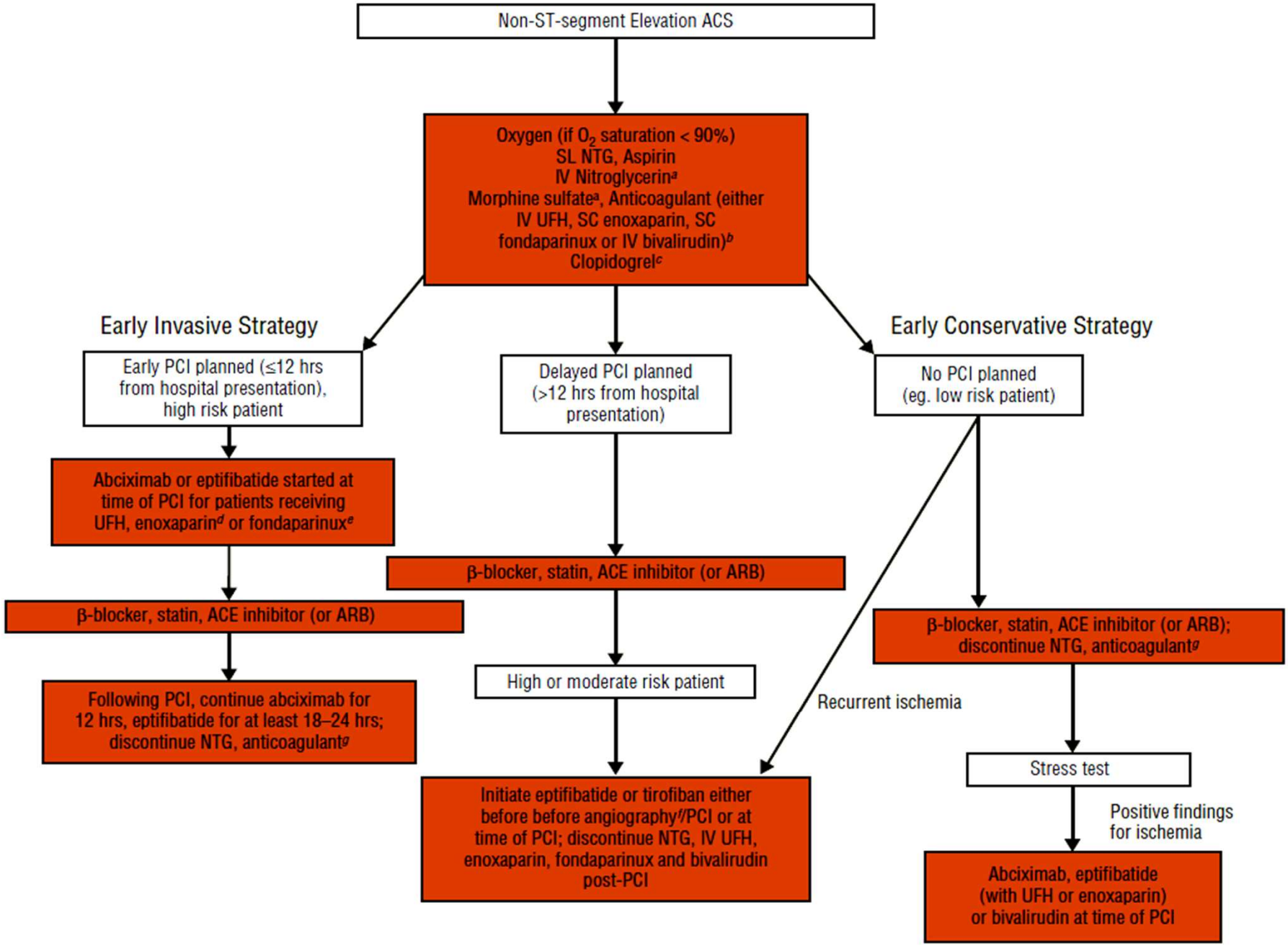
Early pharmacotherapy for non–ST-segment elevation acute coronary syndrome

- According to ACC/AHA practice guidelines, early pharmacotherapy should include:
  - (1) Intranasal oxygen (if oxygen saturation is <90%)
  - (2) SL NTG (IV therapy for selected patients)
  - (3) Aspirin
  - (4) An oral β-blocker (IV therapy optional)
  - (5) An anticoagulant (UFH, LMWH [enoxaparin], fondaparinux, or bivalirudin).
- **Morphine is also administered** to patients with refractory angina, as described previously.
- These agents should be administered early, while the patient is still in the emergency department.

Secondary prevention following MI

- Risk of reinfarction (5% to 15% incidence within the first year) and other complications (e.g., dysrhythmias, heart failure) is there in who survive the acute phase of STEMI

- Outcome can be improved with
  - Risk factor reduction
    - Quit smoking (the goal is total cessation)
    - Appropriate dietary plan for patients with high serum cholesterol
    - Reduce body weight
    - Appropriate control of hypertension, CKD and DM
  - Exercise
  - Long-term therapy with drugs


Non-ST-segment Elevation ACS
Oxygen (if O_2 saturation < 90%)
SL NTG, Aspirin
IV Nitroglycerin[a]
Morphine sulfate[a], Anticoagulant (either IV UFH, SC enoxaparin, SC fondaparinux or IV bivalirudin)[b]
Clopidogrel[c]
Early Invasive Strategy
Early PCI planned (≤12 hrs from hospital presentation), high risk patient
Delayed PCI planned (>12 hrs from hospital presentation)
Early Conservative Strategy
No PCI planned (eg. low risk patient)
Abciximab or eptifibatide started at time of PCI for patients receiving UFH, enoxaparin[d] or fondaparinux[e]
β-blocker, statin, ACE inhibitor (or ARB)
β-blocker, statin, ACE inhibitor (or ARB)
β-blocker, statin, ACE inhibitor (or ARB); discontinue NTG, anticoagulant[g]
Following PCI, continue abciximab for 12 hrs, eptifibatide for at least 18–24 hrs; discontinue NTG, anticoagulant[g]
High or moderate risk patient
Recurrent ischemia
Stress test
Positive findings for ischemia
Initiate eptifibatide or tirofiban either before before angiography[f]/PCI or at time of PCI; discontinue NTG, IV UFH, enoxaparin, fondaparinux and bivalirudin post-PCI
Abciximab, eptifibatide (with UFH or enoxaparin) or bivalirudin at time of PCI

Secondary prevention following MI

- The long-term goals following MI are as follow:

1. Control modifiable CHD risk factors

2. Prevent development of systolic heart failure

3. Prevent recurrent MI and stroke

4. Prevent death, including sudden cardiac death

Secondary prevention following MI

- Pharmacotherapy that has been proven to decrease mortality, heart failure, reinfarction, or stroke should be initiated prior to hospital discharge for secondary prevention.

- Following MI from either STE or NSTE ACS, patients should receive indefinite treatment with aspirin, a β-blocker, and an ACE inhibitor.

- All patients should receive **SL NTG or sub lingual spray and instructions for** use in case of recurrent ischemic chest discomfort.

Secondary prevention following MI

- Selected patients also should be treated with long-term warfarin anticoagulation.
  - Patients with an LV thrombus
  - Patients demonstrating extensive ventricular wall-motion abnormalities on cardiac echocardiogram
  - Patients with a history of thromboembolic disease or chronic atrial fibrillation.

- For all ACS patients, treatment and control of modifiable risk factors, such as hypertension, dyslipidemia, and diabetes mellitus, are essential.

Secondary prevention following MI

- A calcium channel blocker can be used to prevent anginal symptoms in patients who cannot tolerate or have a contraindication to a β-blocker but should not be used routinely in the absence of such symptoms.

Secondary prevention following MI

- For patients with NSTE ACS, **clopidogrel decreases the risk of death, MI,**or stroke.
- Most patients with NSTE ACS should receive clopidogrel, in addition to aspirin, for up to 12 months.
- For patients with STEMI treated medically without revascularization, clopidogrel can be given for 14 to 28 days.
- If a stent has been implanted, clopidogrel can be continued for up to 12 months in patients at low risk for bleeding.

Secondary prevention following MI

- The 2004 ACC/AHA guidelines recommend an aldosterone antagonist in STEMI patients:
  - Without significant renal dysfunction (creatinine <2.5 mg/dL in men and <2.0 mg/dL in women) or hyperkalemia (potassium <5 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an EF<40%, and have either symptomatic heart failure or diabetes

Evaluation of therapeutic outcomes

- Monitoring parameters for efficacy of therapy for both STE and NSTE ACS include:
  - (1) relief of ischemic discomfort
  - (2) return of ECG changes to baseline
  - (3) absence or resolution of heart failure signs.
- Monitoring parameters for adverse effects are dependent upon the individual drugs used.
- In general, the most common adverse reactions from ACS therapies are hypotension and bleeding.

Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding, gastrointestinal upset; baseline CBC and platelet count; CBC platelet count every 6 months
Clopidogrel	Bleeding, TTP (rare), diarrhea, rash	Clinical signs of bleeding ; baseline CBC and platelet count; CBC and platelet count every 6 months following hospital discharge
Unfractionated heparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleedinga ; baseline CBC, platelet count, aPTT and INR; aPTT every 6 hours until target then every 24 hours; daily CBC; platelet count every 2 days (minimum, preferably every day)
Low-molecular-weight heparins (enoxaparin and dalteparin)	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding; baseline CBC, platelet count, SCr, aPTT and INR; daily CBC, platelet count every 2–3 days (minimum, preferably every day); SCr daily
Fondaparinux	Bleeding	Clinical signs of bleeding, baseline CBC, platelet count, INR, SCr, and aPTT; daily CBC and SCr
Bivalirudin	Bleeding	Clinical signs of bleeding baseline CBC, platelet count, INR, SCr, and aPTT; daily CBC and SCr

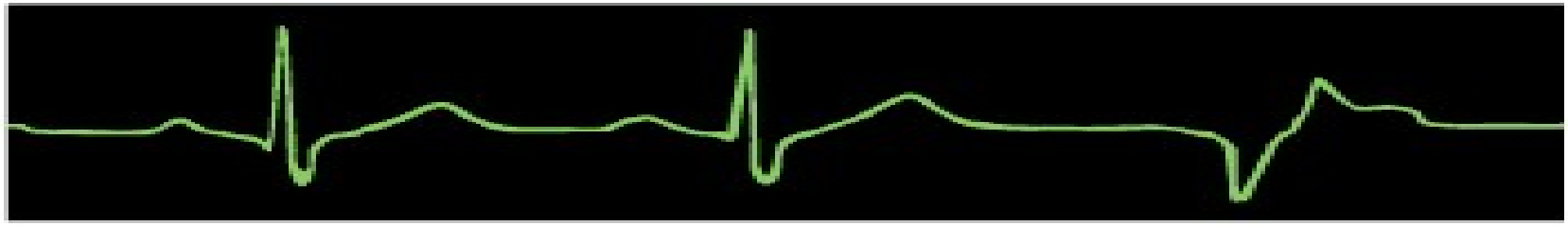
Drug	Adverse Effects	Monitoring
Fibrinolytics	Bleeding, especially intracranial hemorrhage	Clinical signs of bleeding, baseline CBC, platelet count, INR, and aPTT; mental status every 2 hours for signs of intracranial hemorrhage; daily CBC
Glycoprotein IIb/IIIa receptor blockers	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding, baseline CBC and platelet count; daily CBC; platelet count at 4 hours after initiation then daily
Intravenous nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
β-Blockers	Hypotension, bradycardia, heart block, bronchospasm, heart failure, fatigue, depression, sexual dysfunction, nightmares, masking hypoglycemia symptoms in diabetic patients	BP, RR, HR, 12-lead ECG, and clinical signs of heart failure every 5 minutes during bolus intravenous dosing; BP, RR, HR, and clinical signs of heart failure every shift during oral administration during hospitalization, then BP and HR every 6 months following hospital discharge
Diltiazem or verapamil	Hypotension, bradycardia, heart block, heart failure, gingival hyperplasia, constipation	BP and HR and signs of clinical heart failure every shift during oral administration during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
Amlodipine	Hypotension, dependent peripheral edema, gingival hyperplasia	BP every shift during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months

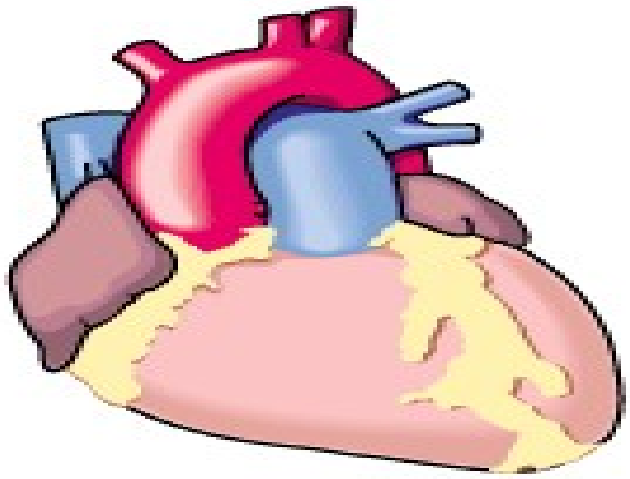
Drug	Adverse Effects	Monitoring
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, angioedema (ACE inhibitors >ARBs)	BP every 2 hours x 3 for first dose, then shift during oral administration during hospitalization, then once every 6 months following hospital discharge; baseline SCr and potassium; daily SCr and potassium while hospitalized, then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in selected patients (e.g., those taking spironolactone or eplerenone or with renal insufficiency); counsel patient on throat, tongue, and facial swelling
Aldosterone antagonists	Hypotension, hyperkalemia, prerenal azotemia	BP and HR every shift during oral administration during hospitalization, then once every 6 months; baseline SCr and serum potassium concentration; SCr and potassium at 48 hours, monthly for 3 months then every 3 months thereafter
Statins	Myalgia, myopathy, elevated LFTs, rhabdomyolysis, teratogenic in first trimester	Baseline LFTs, then repeat LFTs at 6 weeks and when patient titrated to target maintenance dose; if LFTs >3 times upper limit of normal, decrease dose or discontinue; if myalgia and/or brown urine, monitor creatine kinase for rhabdomyolysis
Morphine sulfate	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose

Case Study

- 50. F.G., a 54-year-old man, is brought to the ED by helicopter for treatment of severe, unrelenting chest pain of 2 hours' duration. He has no history of CAD, but cardiac risk factors include a strong positive family history of CAD, a 45-pack-year smoking history, and a 5-year history of hypertension. He is taking oral metoprolol 100 mg BID. Physical examination reveals a middle-aged man in obvious distress with the following vital signs: heart rate, 110 beats/minute; BP, 176/108 mmHg; respiratory rate, 18 breaths/minute; and temperature, 37°C. Normal lung and heart sounds are heard, with the exception of an S_4 gallop. Examination of F.G.'s abdomen and extremities is unremarkable, as is the funduscopic examination. F.G. has received 10 mg morphine sulfate IV and three sublingual 0.4 mg NTG tablets and is still experiencing severe pain that is associated with ST-segment depression. He is placed on oxygen (2 L by nasal prongs) and an NTG infusion (5 mcg/minute). Rapid upward titration of the NTG to 60 mcg/minute alleviates the chest pain. His admitting diagnosis is acute coronary syndrome.
- How do you manage this patient?

Cardiac Arrhythmias





Electrophysiology

☐ *An electrical potential exists across the cell membrane that changes in a cyclic manner related to the flux of ions across the cell membrane, K^+, Na^+, & Ca^{2+}.*

☐ The action potential can be described in five phases.

- **Phase 0**
  - ***Rapid depolarization in response to influx of Na+ ions.***
  - Determines the velocity of impulse conduction
  - Drugs that decrease the rate of phase 0 depolarization (by blocking Na+ channels)
    - Slow impulse conduction though **His-Purkinje system & myocardium.**
- **Phase 1**
  - Rapid (but partial) repolarization takes place
  - Has no relevance to antidysrhythmic drugs

Electrophysiology

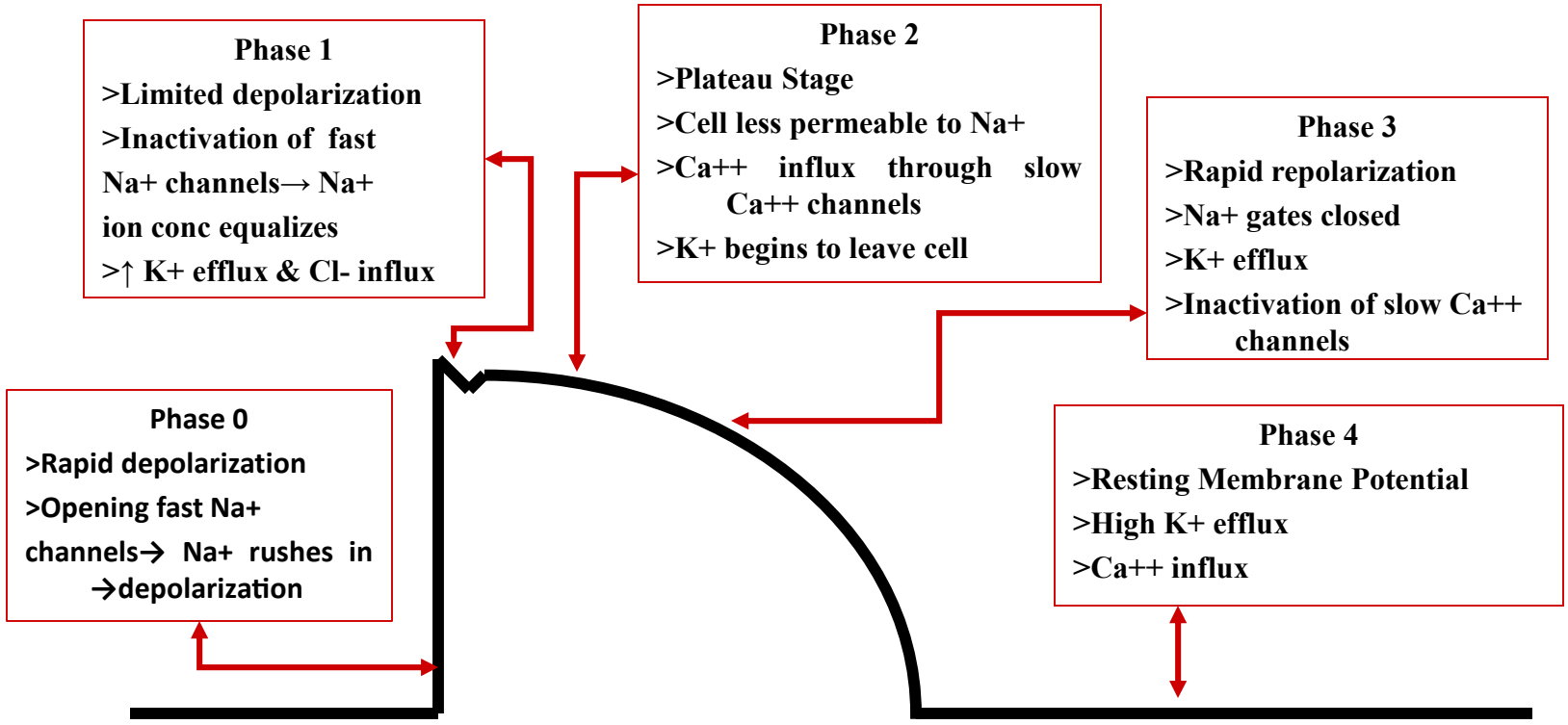
- **Phase 2**
  - Consists of a prolonged plateau in which the membrane potential remains **relatively stable**
  - Calcium enters the cell & promotes **contraction of atrial & ventricular muscle.**
  - Drugs that reduce calcium entry during phase 2 do not influence cardiac rhythm.
    - **Can reduce myocardial contractility.**
- **Phase 3**
  - Rapid repolarization takes place
  - Extrusion of potassium from the cell
  - Relevant in that delay of repolarization prolongs the action potential duration, &
  - Thereby prolongs the effective refractory period (ERP)
    - **ERP** is the time during which a cell is unable to respond to excitation & initiate a new action potential.
- **Phase 4**
  - Two types of electrical activity are possible:
    - The membrane potential may remain stable or
    - The membrane may undergo spontaneous depolarization

Electrophysiology

- **Slow Potentials**
  - Occur in cells of the SA node & AV node
  - Three features of special significance
    - Phase 0—slow depolarization
      - Mediated by **calcium influx**
      - Calcium influx is slow, the rate of depolarization is slow; &
        - These potentials **conduct slowly**
        - Explains why impulse conduction through the **AV node is delayed.**
      - *Therapeutic significance in that drugs that suppress calcium influx during phase 0.*
        - **Can slow (or stop) AV conduction**
    - Phase 1, 2, & 3
      - Phase 1 absent
      - Phase 2 & 3 not significant
    - Phase 4—depolarization
      - Spontaneous **phase 4 depolarization**
      - Under normal conditions,
        - The rate of phase 4 depolarization in cells of the SA node is faster than in all other cells of the heart.
        - The SA node discharges first & determines HR.
        - Is referred to as the **cardiac *pacemaker.***

Electrophysiology

Phases of Action Potential



Electrophysiology

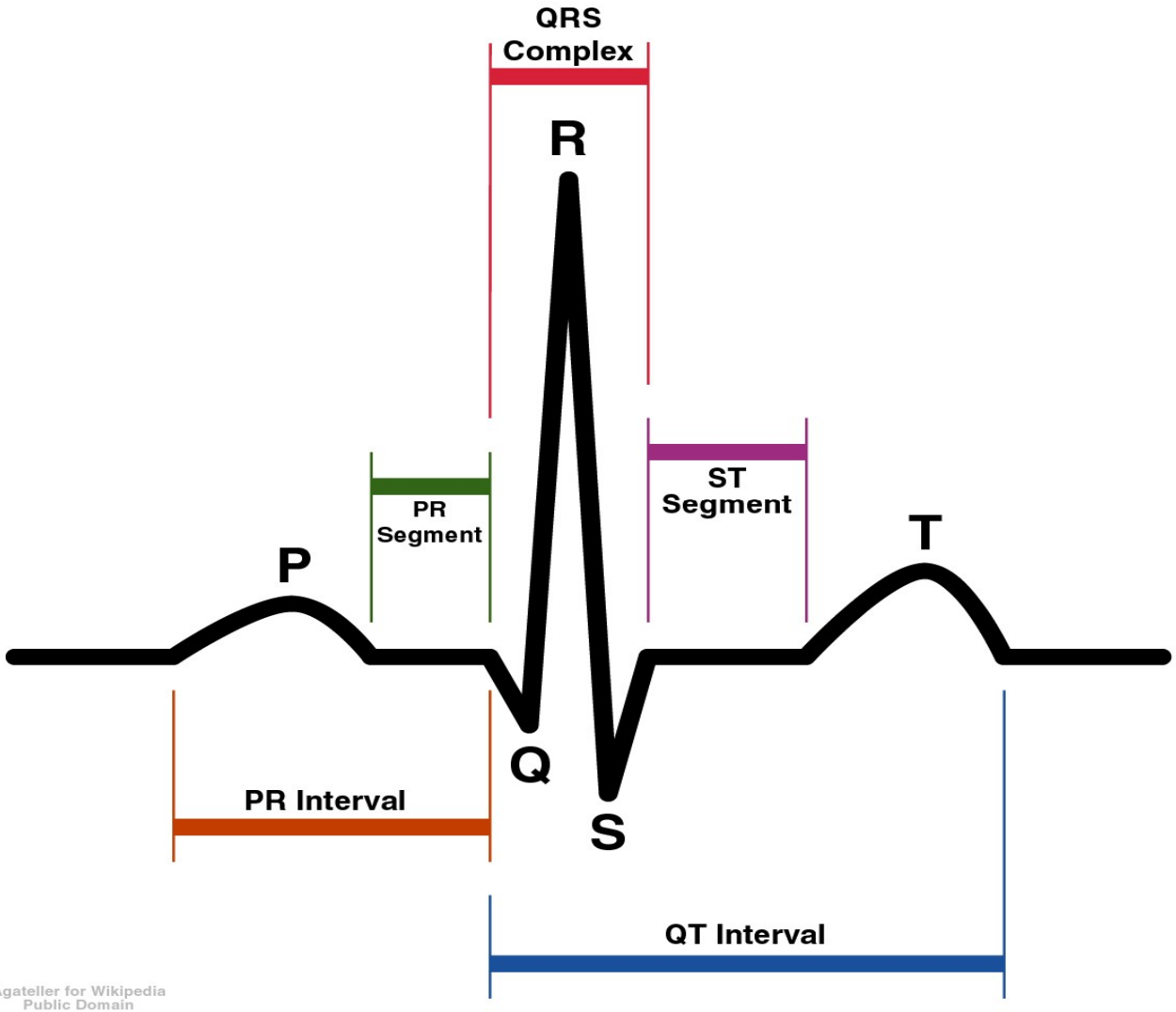
- ECG can be used as a rough guide to some cellular properties of cardiac tissue:
- HR reflects sinus node automaticity.
- PR-interval duration reflects AV nodal conduction time.
- QRS duration reflects conduction time in the ventricle.
- The QT interval is a measure of ventricular APD.

ECG (EKG) showing wave segments

RMP = 61.5 log [K+] outside)

[K+] inside

- For example, this specific pump (in addition to other systems) attempts to maintain the intracellular Na+ concentration at 5 to 15 mEq/L & the extracellular Na+ concentration at 135 to 142 mEq/L; the intracellular potassium concentration at 135 to 140 mEq/L & the extracellular potassium concentration at 3 to 5 mEq/L.



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ANTIARRHYTHMIC DRUGS

CLASS I (Na^+ channel blockers)

- *Disopyramide (IA)*
- *Flecainide (IC)*
- *Lidocaine (IB)*
- *Mexiletine (IB)*
- *Procainamide (IA)*
- *Propafenone (IC)*
- *Quinidine (IA)*
- *Tocainide (IB)*

CLASS II (β-adrenoreceptor blockers)

- *Esmolol*
- *Metoprolol*
- *Propranolol*

CLASS III (K^+ channel blockers)

- *Amiodarone*
- *Dofetilide*
- *Sotalol*

CLASS IV (Ca^{2+} channel blockers)

- *Diltiazem*
- *Verapamil*

OTHER ANTI-ARRHYTHMIC DRUGS

- *Adenosine*
- *Digoxin*

Antiarrhythmic Drugs

CLASS I: Na+ Channel Blocking Drugs

- **IA** **-Lengthen APD (longer QT interval)**
  -Moderate slowing of phase 0 (medium Na blockade)
  -Quinidine, Procainamide, Disopyramide
- **IB** **-Shorten APD**
  -Minimal slowing of phase 0 (least Na blockade)
  -Therefore shorter QT interval
  -Lidocaine, Mexiletene, Tocainide, Phenytoin
- **IC** **-No effect APD**
  -Maximal slowing of phase 0 (greatest Na blockade)
  -Flecainide, Propafenone, Moricizine
- ***Constitutes the largest group of antidysrhythmic drugs***

Antiarrhythmic Drugs
Class II: Beta-blocking Agents

- Decrease AV nodal conduction
- In the SA node, they reduce automaticity
- Increase PR interval & prolong AV nodal refractoriness
- Reduce adrenergic activity
- In the atria & ventricles, they reduce contractility
  - Reduce calcium entry *(during fast & slow potentials)* &
  - Depress phase 4 depolarization (in slow potentials only)
- *Propranolol, Esmolol, Metoprolol, Sotalol*

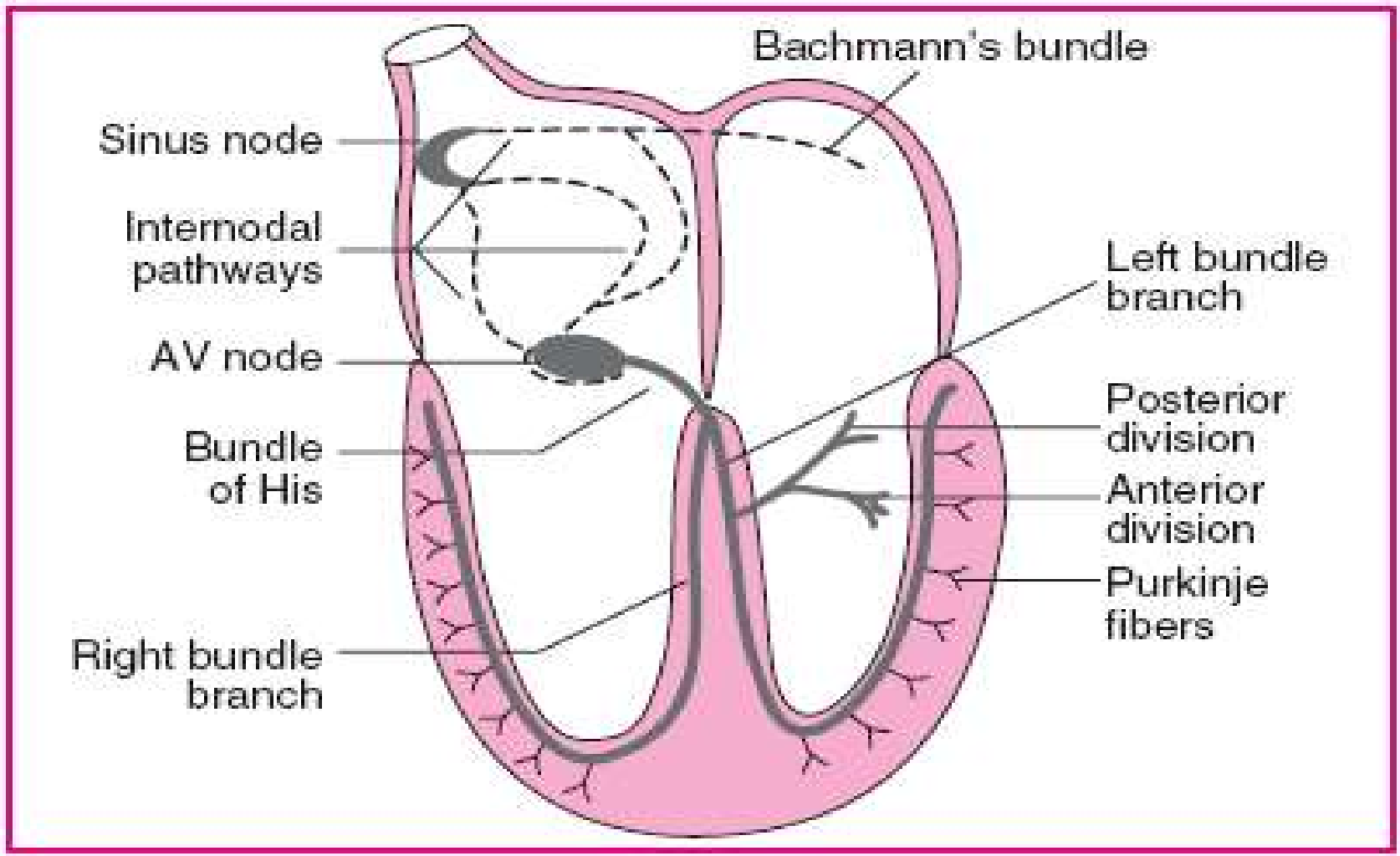
Antiarrhythmic Drugs
Class III: Potassium Channel Blockers

- **Prolong effective refractory period by prolonging action Potential.**
  - ***Amiodarone***
  - ***Bretylium***
  - ***Sotalol***
  - ***Ibutilide***
  - ***Dofetilide***

Antiarrhythmic Drugs
Class IV: Calcium Channel Blockers

- Blocks cardiac calcium currents
  - Velocity of AV nodal conduction decreases,
    - PR interval increase
  - Increase refractory period
    - Esp. in Ca^{2+} dependent tissues (i.e. **AV node**)
    - Antidysrhythmic benefits derive from suppressing AV nodal conduction
- ***Verapamil, Diltiazem***

Cardiac Conduction System



Classification

1. **Supraventricular tachycardia (SVT)**

– Tachyarrhythmias that either **originate** from or **incorporate** SV tissue in a reentrant circuit.

– **PSVTs**: group of SVTs that are x-zed by: Clinical syndrome of rapid, regular tachycardia with an abrupt onset and termination

– Other forms: atrial flutter, atrial fibrillation…

– Non-sustained forms: APCs, AVJPCs(AV Junctional premature contractions)

2. **Ventricular tachyarrhythmia:** origin

- ❑ Ventricular tachycardia
- ❑ Ventricular fibrillation
- ❑ VPcs

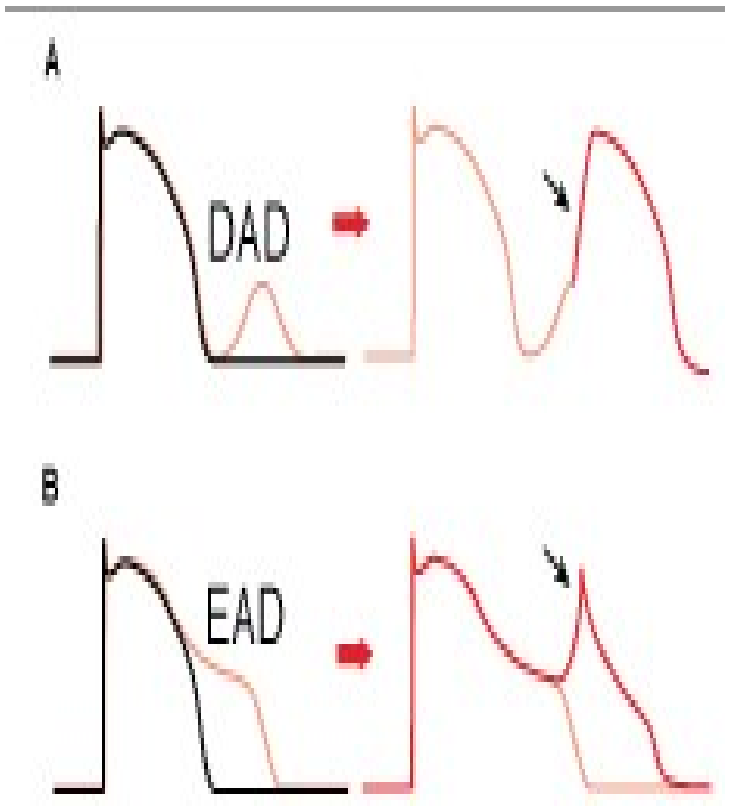
Mechanisms Of Tachyarrhythmia

1. **Disorders of impulse formation**
   - Abnormal automaticity
   - Triggered activity
2. **Disorders of impulse conduction**
   - Reentry

- Abnormal automaticity (means pacing is not by SA node)
  - Ischemia
  - Metabolic disturbance, or
  - Pharmacologic manipulation(**Atropine, Isoprenaline**)
  - **Triggered activity:** refers to pacemaker activity that is dependent on **after depolarization** from a prior impulse or series of impulses.
  - ***Reentry: impulse propagation in a circuit pathway in a cardiac tissue.***

Triggered Activity

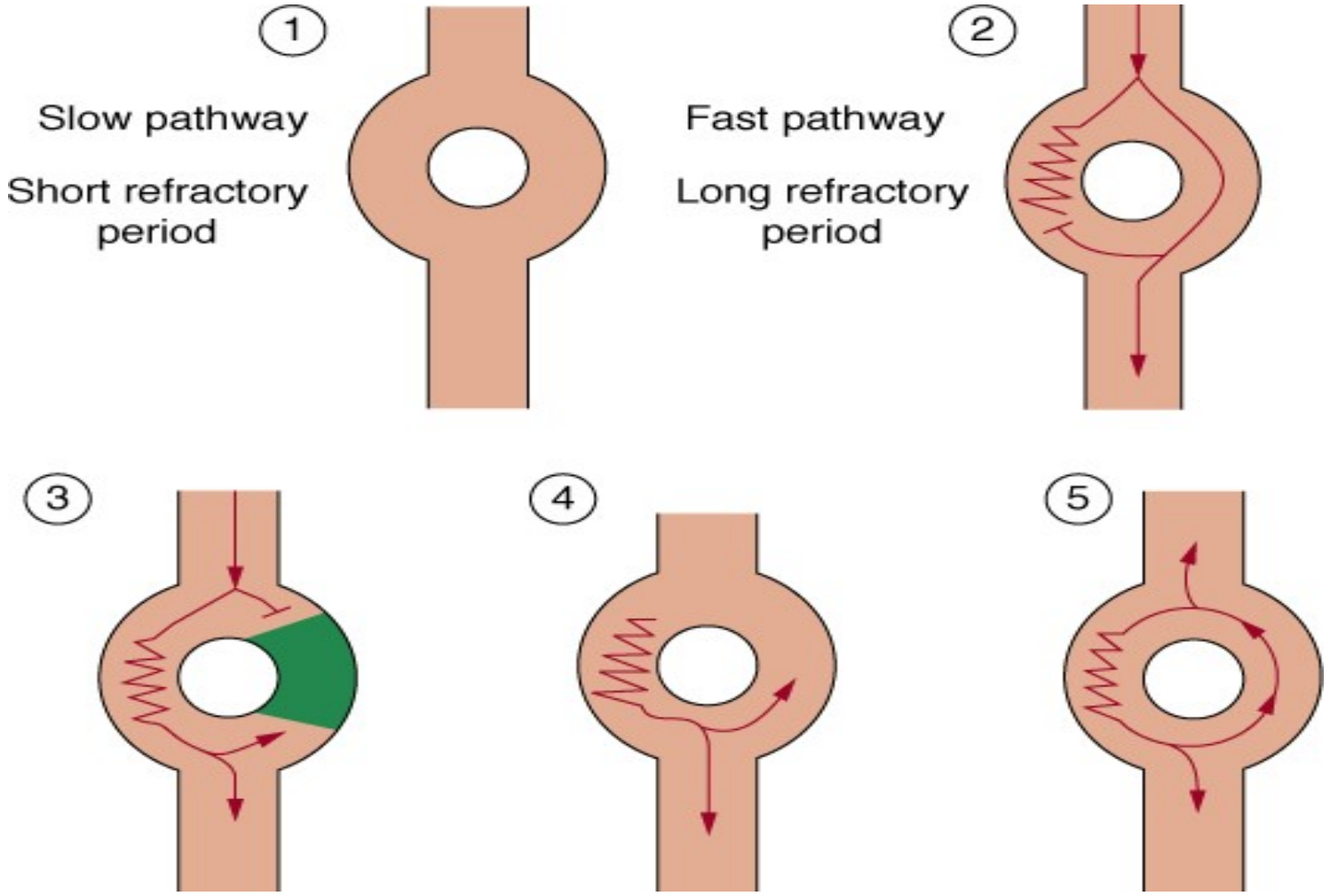
- Triggered automaticity is also a possible mechanism for abnormal impulse generation. Briefly, triggered automaticity refers to transient membrane depolarizations that occur during repolarization (early after-depolarizations [EADs]) or after repolarization(late after depolarizations[LADs]) but prior to phase 4 of the action potential.
- After-depolarizations may be related to abnormal calcium and sodium influx during or just after full cellular repolarization.



Reentry

- **In order for reentry to occur, three conditions must be met:**
  - Two functionally distinct conducting pathways.
  - Unidirectional conduction block in one of the pathways.
  - Slow conduction down the unblocked pathway, which allows the blocked pathway time to **recover excitability** and sustain the arrhythmia.

Reentry


1
Slow pathway
Short refractory period
2
Fast pathway
Long refractory period
3
4
5

Atrial Fibrillation & Atrial Flutter Management

- Atrial fibrillation & atrial flutter are common supraventricular tachycardias.
- **Atrial fibrillation** is characterized as an extremely rapid (atrial rate of 400 to 600 beats/min) & disorganized atrial activation.
- **Atrial flutter** occurs less frequently than AF, This arrhythmia is characterized by rapid (270 to 330 atrial beats/min) but regular atrial activation.
- With signs &/or symptoms of hemodynamic instability (e.g., severe hypotension, angina, or pulmonary edema , qualifies as a medical emergency.

➢ DCC is indicated as first-line therapy in an attempt to immediately restore sinus rhythm (without regard to the risk of thromboembolism).

Atrial Fibrillation & Atrial Flutter
Acute Treatment

- If patients are hemodynamically stable, there is no emergent need to restore sinus rhythm.
- ➢ Instead, the focus should be directed toward controlling the patient's ventricular rate.
- Achieving adequate ventricular rate control is a treatment goal for all patients with AF.
- Initial therapy, drugs that slow conduction & increase refractoriness in the AV node (e.g., β-*blockers, nondihydropyridine CCBs,* or digoxin).
- Use of digoxin for achieving ventricular rate control, especially in patients with normal LV systolic function (left ventricular ejection fraction [LVEF] >40%) not recommended.

Atrial Fibrillation & Atrial Flutter
Acute Treatment

- its relatively slow onset & its inability to control the HR during exercise.
- Digoxin , ineffective for controlling ventricular rate under conditions of increased sympathetic tone (i.e., surgery, thyrotoxicosis).
- ✓ it slows AV nodal conduction primarily through vagotonic mechanisms.
- ✓ IV β-*blockers (propranolol,* metoprolol, esmolol), diltiazem, or verapamil is preferred.
- ✓ A relatively quick onset & can effectively control the ventricular rate at rest & during exercise.
- β- blockers are also effective for controlling ventricular rate under conditions of increased sympathetic tone.

Atrial Fibrillation & Atrial Flutter
Acute Treatment

- Recent guidelines for the treatment of AF, drug selection to control ventricular rate in the acute setting should be primarily based on the patient's LV function.
- In patients with normal LV function (LVEF >40%), IV β-*blockers, diltiazem, or* verapamil is recommended as first-line therapy to control ventricular Rate.
- In patients with LV dysfunction (LVEF ≤40%), IV diltiazem or verapamil should be avoided because of their potent negative inotropic effects.
- IV β-*blockers should be used with caution in this* patient population & should be avoided if patients are in the midst of an episode of decompensated HF.

Atrial Fibrillation & Atrial Flutter
Acute Treatment

- Exacerbation of HF symptoms, IV administration of either digoxin or amiodarone should be used as first-line therapy to achieve ventricular rate control.
- IV amiodarone can also be used in patients who are refractory to or have C/Is to β-*blockers,* nondihydropyridine CCBs, & digoxin.
- But use of amiodarone for controlling ventricular rate may also stimulate the conversion of AF to sinus rhythm, & place the patient at risk for a thromboembolic event.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- Because a rhythm control strategy does not confer any advantage over a rate-control strategy in the management of AF.
- Now it remains acceptable to allow patients to remain in AF, while being chronically treated with AV nodal-blocking agents to achieve adequate ventricular rate control (e.g., HR <80 beats/min at rest & <100 beats/min during exercise).
- The selection of an AV nodal-blocking agent to control ventricular rate in the chronic setting primarily based on the patient's LV function.

✓ In patients with normal LV function (LVEF >40%), oral β-*blockers, diltiazem, or verapamil are* preferred over digoxin because of their relatively quick onset & maintained efficacy during exercise.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- ✓ When adequate ventricular rate control cannot be achieved with one of these agents, the addition of digoxin may provide an additive lowering of the HR.
- Verapamil & diltiazem should not be used in patients with LV dysfunction (LVEF ≤40%).
- ✓ β-*blockers (i.e., metoprolol,* Carvedilol, or bisoprolol) & digoxin are preferred in these patients, as these agents are also concomitantly used to treat chronic HF;
- ✓ If possible, β-*blockers should be considered over digoxin in this* situation because of their survival benefits in patients with LV systolic dysfunction.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- If patients are having an episode of decompensated HF, digoxin is preferred as first-line therapy to achieve ventricular rate control.
- In those patients in whom it is decided to restore sinus rhythm, one must consider that this very act (regardless of whether an electrical or pharmacologic method is chosen) places the patient at risk for a thromboembolic event.
- the return of sinus rhythm restores effective contraction in the atria, which may dislodge poorly adherent thrombi.
- Administering antithrombotic therapy prior to cardioversion not only prevents clot growth & the formation of new thrombi but also allows existing thrombi to become organized & well-adherent to the atrial wall.

ATRIAL FIBRILLATION & ATRIAL FLUTTER
chronic management

- Patients become at increased risk of thrombus formation & a subsequent embolic event if the duration of the AF exceeds 48 hours.
- Patients with AF for longer than 48 hours or an unknown duration should receive warfarin treatment (target INR 2.5; range: 2.0 to 3.0) for at least 3 weeks prior to cardioversion.
- After restoration of sinus rhythm, full atrial contraction returns gradually to a maximum contractile force over a 3- to 4-week period.

✓ Warfarin continued for at least 4 weeks after effective cardioversion & return of sinus rhythm.

- Methods of restoring sinus rhythm in patients with AF or atrial flutter:

✓ Pharmacologic cardioversion &

✓ DCC.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- The disadvantages of pharmacologic cardioversion are the risk of significant side effects.

✓ The inconvenience of drug–drug interactions (e.g., digoxin–amiodarone), &

✓Drugs are generally less effective when compared to DCC.

- The advantages of DCC are that it is quick & more often successful (80% to 90% success rate).
- Pharmacologic cardioversion appears to be most effective when initiated within 7 days after the onset of AF.
- Single, oral loading doses of propafenone (600 mg) & flecainide (300 mg) are effective for conversion of recent onset AF & provide a simple regimen.
- A method called the “pillin- the-pocket” approach was recently endorsed by the treatment guidelines.

ATRIAL FIBRILLATION & ATRIAL FLUTTER
chronic management

- Outpatient, patient-controlled self administration of a single, oral loading dose of either flecainide or propafenone .
- A relatively safe & effective approach for the termination of recent-onset AF in patient population that does not have sinus or
- AV node dysfunction, bundle-branch block, QT interval prolongation, or structural heart disease.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- *In patients with AF that is longer than 7 days in duration, only* ***dofetilide, amiodarone, & ibutilide have proven efficacy for cardioversion.***
- Selection of an antiarrhythmic drug should be based on whether the patient has structural heart disease (e.g., LV dysfunction, coronary artery disease, valvular heart disease, LV hypertrophy).
- In the absence of any type of structural heart disease, the use of a single, oral loading dose of flecainide or propafenone is a reasonable approach for cardioversion.

Atrial Fibrillation & Atrial Flutter
Chronic Management

- In patients with underlying structural heart disease, these antiarrhythmics should be avoided, & amiodarone or dofetilide should be used instead.
- amiodarone can be administered safely on an outpatient basis because of its low proarrhythmic potential, dofetilide can only be initiated in the hospital.
- patient's ventricular rate should be adequately controlled with AV nodal-blocking drugs prior to administering a type Ic (or Ia) antiarrhythmic for cardioversion.
- The types Ia & Ic agents may paradoxically increase ventricular response.

Ventricular Arrhythmias

- The common ventricular arrhythmias include: (a) PVCs, (b) VT, & (c) VF.
- Premature ventricular complexes often cause no symptoms or only **mild palpitations.**
- Ventricular tachycardia may be a life-threatening situation associated with **hemodynamic collapse or may be totally asymptomatic.**
- Ventricular fibrillation, by definition, is an acute medical emergency necessitating **CPR.**

Ventricular Tachycardia

- An acute episode of VT precipitated by severe electrolyte abnormalities (hypokalemia), hypoxemia, or digitalis toxicity, or (most commonly) may occur during an acute MI or ischemia complicated by HF.
- VT occurs during the first 24 hours of an acute MI, it will probably not reappear on a chronic basis after the infracted area has been reperfused or healed with scar formation.
- In contrast, some patients have a chronic recurrent form of VT that is almost always associated with some type of underlying structural heart disease.

✓ Dilated cardiomyopathy or

✓ Remote MI with a LV aneurysm.

Ventricular Tachycardia

- Acute episode of VT (with a pulse) with severe symptoms (i.e., severe hypotension, angina, pulmonary edema),

✓ Synchronized DCC should be delivered immediately to attempt to restore sinus rhythm.

- Patients presenting with an acute episode of VT (with a pulse) associated with only mild symptoms can be initially treated with antiarrhythmic drugs.

✓ IV amiodarone is now recommended as first-line antiarrhythmic therapy in this situation.

Ventricular Tachycardia

- IV amiodarone begins with a 150 mg bolus over 10 minutes, followed by a continuous IV infusion of 1 mg/min for six hours & 0.5 mg/min thereafter.
- Repeated boluses can be given over 10 minutes every 10 to 15 minutes to a maximum total dose of 2.2 g in 24 hours. The blood pressure must be carefully monitored because the diluent can cause hypotension.
- IV procainamide was shown to be superior in terminating VT than lidocaine .

Ventricular Tachycardia

- IV **Procainamide** can be administered in a number of ways.

✓ The standard method is an infusion of 20 mg/min until the arrhythmia terminates, hypotension ensues, the QRS is prolonged by more than 50 percent, or a total of 17 mg/kg (1.2 g for a 70 kg patient) has been given.

- **Lidocaine** is given by IV push in a dose of 0.5 to 0.75 mg/kg; this dose is repeated every 5 to 10 minutes as needed.
- At the same time, a continuous IV infusion of 1 to 4 mg/min is begun. The maximum total dose is 3 mg/kg over one hour.

Ventricular Tachycardia

- Once an acute episode of sustained VT has been successfully terminated by electrical or pharmacologic means & an acute MI has been ruled out, the possibility of a patient having recurrent episodes of VT should be considered.
- If chronic management is required, amiodarone therapy is superior in preventing **SCD** & recurrences of severe ventricular arrhythmias at all time points.
- Patients with pulseless VT are treated as if they had ventricular fibrillation.

Ventricular Fibrillation

- VF is electrical anarchy of the ventricle resulting in no cardiac output & cardiovascular collapse.
- Patients who die abruptly (within 1 hour of initial symptoms) & unexpectedly (i.e., “sudden death”) usually have VF recorded at the time of death.
- Sudden cardiac death accounts for about 330,000 deaths per year in the United States.
- Of all patients who die as a result of an acute MI, approximately 50% die suddenly prior to hospitalization.
- VF associated with acute MI can be subdivided into two types: primary VF & complicated or secondary VF.

✓ Primary VF occurs in an uncomplicated MI not associated with HF;

✓ Secondary VF occurs in an MI complicated by HF.

Ventricular Fibrillation
Acute Management

- Patient with pulseless VT or VF (with or without associated myocardial ischemia)
- ✓ Receives five cycles (or 2 minutes) of CPR (one cycle of CPR = 30 chest compressions followed by 2 breaths) should be given before defibrillation.
- ✓ After delivery of the initial shock, five cycles of CPR should be delivered, followed by a check of the patient's pulse & rhythm.
- If pulseless VT/VF is still present, another shock can be delivered, followed by five cycles of CPR.
- This general sequence of providing shocks followed by CPR can be followed as long as the patient remains in pulseless VT/VF.
- Epinephrine or vasopressin can be administered if pulseless VT/VF persists after delivery of one or two shocks plus CPR.

Ventricular Fibrillation
Acute Management

- Epinephrine can be administered every 3 to 5 minutes while the patient remains in pulseless VT/VF.
- If pulseless VT/VF persists after delivery of two or three shocks plus CPR & after administration of a vasopressor, antiarrhythmic therapy can then be initiated.
- IV amiodarone continues to be the antiarrhythmic drug of first choice in patients with pulseless VT/VF.
- Significantly more patients with out-of-hospital pulseless VT/ VF who received 300 mg of IV amiodarone survived to hospital admission.
- IV amiodarone was significantly more effective than lidocaine in increasing survival to hospital admission in patients with out-of-hospital VF.

Ventricular Fibrillation
Long Term Management

- Episode of pulseless VT/VF was associated with acute ischemia,

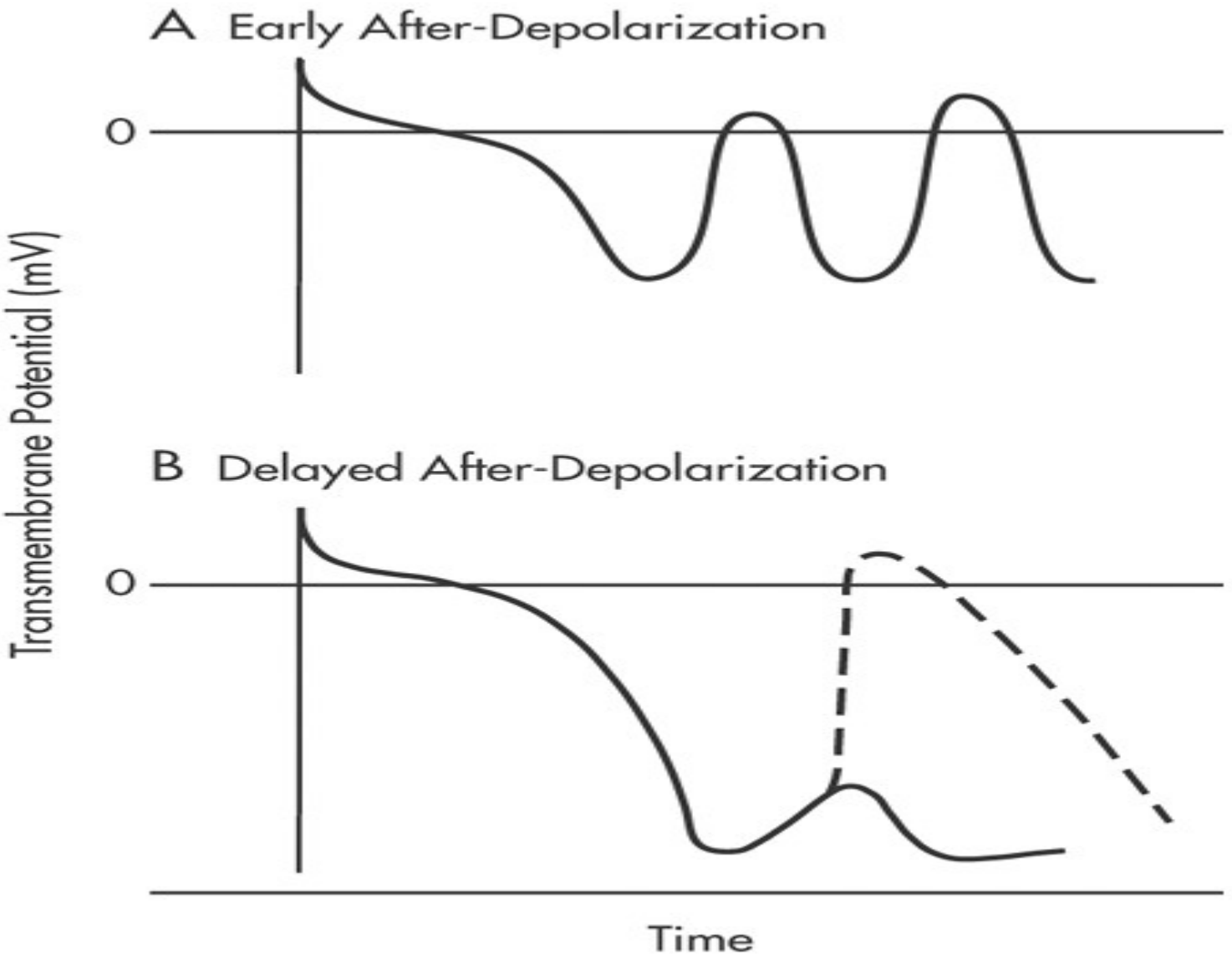
✓ Long-term antiarrhythmic drugs are probably unnecessary provided that the patient undergoes successful revascularization;

✓ Patient should be monitored closely for recurrence of VT &/or VF.

❑ The pulseless VT/VF was not associated with acute MI (or a known precipitating factor), the patient should undergo ICD implantation.

Torsade de Pointes

- TdP is a rapid form of **polymorphic VT** that is associated with evidence of delayed ventricular repolarization (**long QT interval or prominent U waves)** on ECG.
- A long QT interval is crucial to the diagnosis of TdP.
- Drugs or diseases that delay repolarization by influencing ion movement (usually by blocking potassium efflux) provoke EADs(early after depolarizations).


A Early After-Depolarization
0
B Delayed After-Depolarization
0
Transmembrane Potential (mV)
Time

Torsade de Pointes

- The underlying etiology in both cases is delayed ventricular repolarization due to blockade of potassium conductance.
- The type **Ia** antiarrhythmic drugs (especially **quinidine)** & type **III** IKr blockers are most notorious for precipitating TdP; the types Ib & Ic antiarrhythmic drugs rarely, if ever, cause TdP.
- Most antiarrhythmic drugs with Kr blocking activity cause TdP in approximately 2% to 4% of patients, with the exception being **amiodarone (<1%).**

Torsade de Pointes

- Drug-induced TdP have been identified & can be summarized as follows

(a) high dosages or plasma concentrations of the offending agent ("dose-related") (except for quinidine-induced TdP, which tends to occur more frequently at low-to-therapeutic concentrations;

(b) concurrent structural heart disease (e.g., ischemic heart disease, HF, &/or LV hypertrophy);

(c) evidence of mild delayed repolarization (prolonged QT interval) at baseline;

(d) evidence of a prolonged QT interval shortly after initiation of the offending agent;

(e) concomitant electrolyte disturbances such as hypokalemia or hypomagnesemia;

Torsade de Pointes

- Inhibition (drug-induced) of IK current & manifests as QT interval prolongation on the ECG.
- ✓ the extent of QT interval prolongation has been used as a measurement of risk of TdP;
- ✓ however, considerable controversy exists. Amiodarone, for example, commonly causes significant QT prolongation but is a relatively infrequent cause of TdP.
- QT interval should be measured & monitored in all patients prescribed drugs that have a high potential for causing TdP.
- Patients with a baseline **QTc** interval (QT interval corrected for HR) >**450 msec** should not be given these agents;
- an increase in the QTc interval to **≥560 msec** after the initiation of the drug is an indication to discontinue the agent or, at least, to reduce its dosage & carefully observe & monitor.

Torsade de Pointes

- Drug-induced TdP has become an extremely visible hazard plaguing new drugs, sometimes resulting in public health disasters.
- **For instance, six drugs (cisapride, astemizole, terodiline, levomethadyl, grepafloxacin, & terfenadine) have been withdrawn from the market in the United States because of TdP.**
- Striking examples was with regard to the popular nonsedating antihistamine, terfenadine.

✓ Terfenadine is a potent **Kr** blocker but is rapidly metabolized by CYP3A4 to an active moiety (fexofenadine) that is not associated with delayed repolarization.

- In the presence of drugs that block the CYP3A4 isoenzyme (e.g., ketoconazole, erythromycin, diltiazem), accumulation of the parent compound, terfenadine, causes clinically significant blockade of Kr that could result in TdP & even death.

Torsade de Pointes

- For an acute episode of TdP, most patients will require & respond to DCC.
- ✓ after the initial restoration of a stable rhythm, therapy designed to prevent recurrences of TdP should be instituted.
- Drugs that further prolong repolarization such as IV procainamide are absolutely contraindicated. Lidocaine is usually ineffective.
- Although there are no true efficacy trials, IV magnesium sulfate, by suppressing EADs, is now considered the drug of choice in preventing recurrences of TdP.
- If IV magnesium sulfate is ineffective, treatment strategies designed to increase HR, shorten ventricular repolarization, & prevent the pause dependency should be initiated.
- isoproterenol or epinephrine infusion)can be initiated for this purpose.
- All agents that prolong QT interval should be discontinued & exacerbating factors (such as hypokalemia or hypomagnesemia) should be corrected.

Bradyarrhythmias

Sinus Bradycardia

- Sinus bradyarrhythmias (HR <60 beats/min) is a common finding, especially in young, athletically active individuals, & usually is neither symptomatic nor requires therapeutic intervention.
- Sinus node dysfunction is usually reflective of diffuse conduction disease, & accompanying AV block is relatively common.

Sinus Bradycardia

- The treatment of sinus node dysfunction involves the elimination of symptomatic bradycardia & the possibility of managing alternating tachycardias such as AF.
- the long-term therapy of choice is a permanent ventricular pacemaker.
- Drugs that are commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker.

Sinus Bradycardia

- drugs that depress SA or AV nodal function, such as β-*blockers & nondihydropyridine* CCBs, may also significantly exacerbate bradycardia.
- Even agents with indirect sympatholytic actions, such as methyldopa & clonidine, may worsen sinus node dysfunction. The use of digoxin in these patients is controversial, but in most cases, it can be used safely.

Atrioventricular Block

- Conduction delay or block may occur in any area of the AV conduction system: the AV node, the His bundle, or the bundle branches.
  - If impulse conduction is delayed (but not prevented entirely), the block is termed **first degree.**
  - If some impulses pass through the node but others do not, the block is termed second degree.
- Third-degree AV block is complete heart block where AV conduction is totally absent (AV dissociation).

Atrioventricular Block

- If Patient with third-degree AV block develop signs or symptoms of poor perfusion (e.g., altered mental status, chest pain, hypotension, shock) associated with bradycardia or AV block, transcutaneous pacing should be initiated immediately
- IV atropine (0.5 mg given every 3 to 5 minutes, up to 3 mg total dose) should be given as the leads for pacing are being placed.

✓ facilitates the effectiveness of transcutaneous pacing.

- In the past, isoproterenol infusion was frequently chosen for this purpose but is now not recommended because of its vasodilating properties & its ability to increase myocardial oxygen consumption (particularly during acute MI).
- patients not respond to atropine, transcutaneous pacing is usually indicated.

Atrioventricular Block

- Sympathomimetic infusions such as epinephrine (2 to 10 mcg/min) or dopamine (2 to 10 mcg/kg/min) can also be used in the event of atropine failure & are particularly effective in sinus bradycardia/arrest & AV nodal block.
- These agents usually do not help when the site of AV block is below the AV node (e.g., Mobitz II or trifascicular AV block).

TABLE 19-13 Forms of Atrioventricular Block

Type	Criteria	Site of Block
First-degree block	Prolonged PR interval (>0.2 sec); 1:1 AV conduction	Usually AVN
Second-degree block		
Mobitz I	Progressive PR prolongation until QRS is dropped; <1:1 AV conduction	AVN
Mobitz II	Random nonconducted beats (absence of QRS); <1:1 AV conduction	Below AVN
Third-degree block	AV dissociation Absence of AV conduction	AVN or below

AV, atrioventricular; AVN, atrioventricular node.

Using intracardiac His bundle ECGs, the actual site of conduction delay/block can be correlated to the above diagnosis.

Atrioventricular Block

- patients with bradycardia or AV block present with signs & symptoms of adequate perfusion, no therapy other than close observation is recommended.

- Patients with chronic symptomatic AV block should be treated with the insertion of a permanent pacemaker. Patients without symptoms can sometimes be followed closely without the need for a pacemaker.

Pharmacotherapy of Stroke

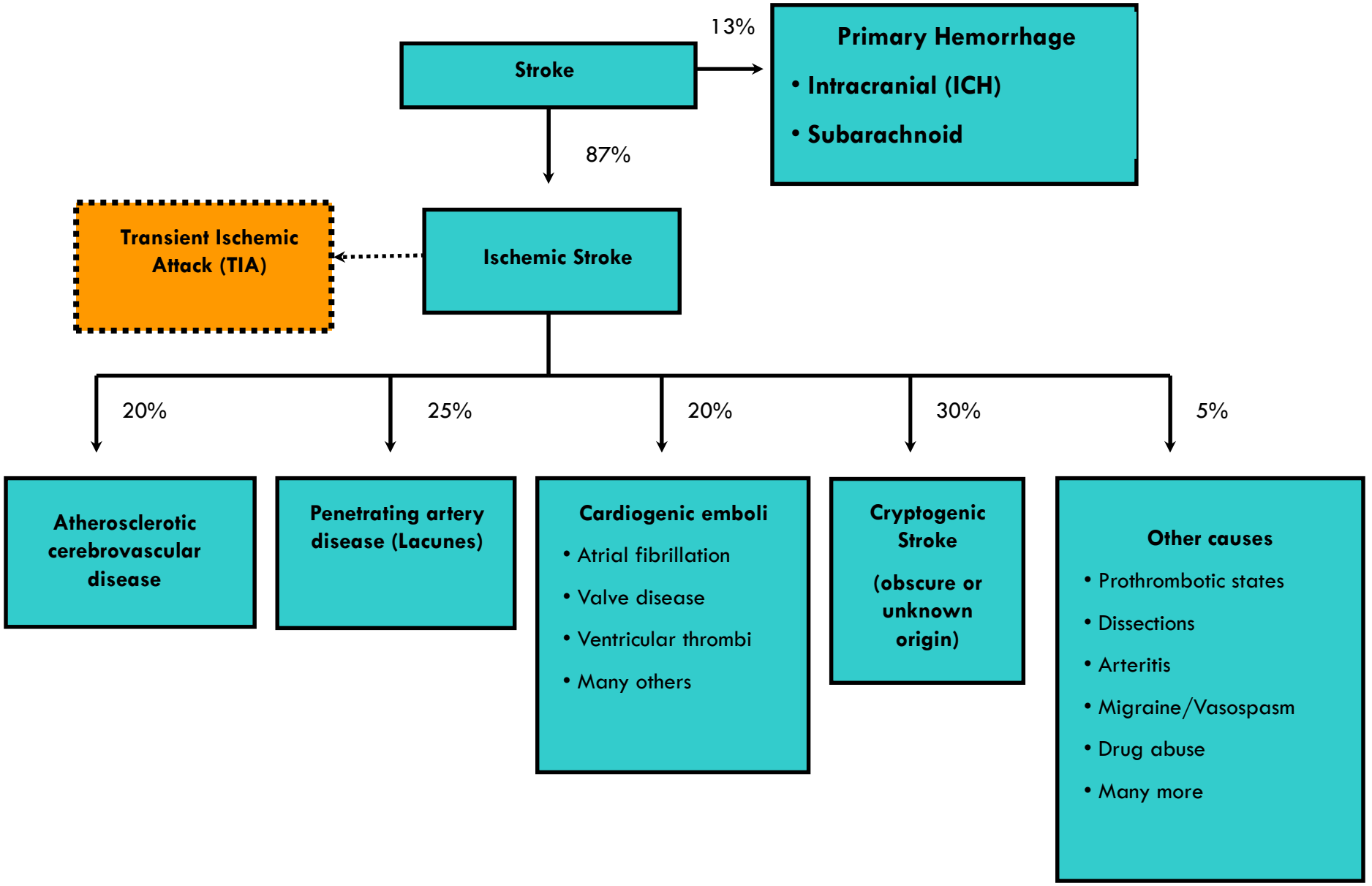
Definition

- Stroke is a term used to describe
  - an abrupt onset of focal neurologic deficit that lasts **at least 24 hours** and is presumed to be of **vascular origin**
  - Second leading cause of death next to heart disease
  - Stroke can be either **ischemic** or **hemorrhagic**
    - Diametrically opposite conditions
    - Block in a blood vessel supplying to a part of brain
    - A bleed in the brain
- Transient ischemic attacks (TIAs) are
  - Focal ischemic neurologic deficits lasting **less than 24 hours** and usually less than 30 minutes.

Pathophysiology
Risk Factors For Stroke

- **Non-modifiable risk factors**
  - **Age (> 55 years)**
  - Male gender
  - Race (African American, Asian, Hispanic)
  - Family history of stroke
  - **Low birth weight**
- **Major modifiable risk factors**
  - **Hypertension**
  - **Cardiac disease** (especially atrial fibrillation)
  - **Diabetes mellitus**
  - **OCs(high estrogen content)**
  - **Dyslipidemia**
  - **Lifestyle factors**
    - **Cigarette smoking**
    - **Excessive alcohol use**
    - **Physical inactivity**
    - **Obesity**
    - **Diet**
    - **Cocaine and intravenous drug use**
    - **Low socioeconomic status**

Stroke Classification



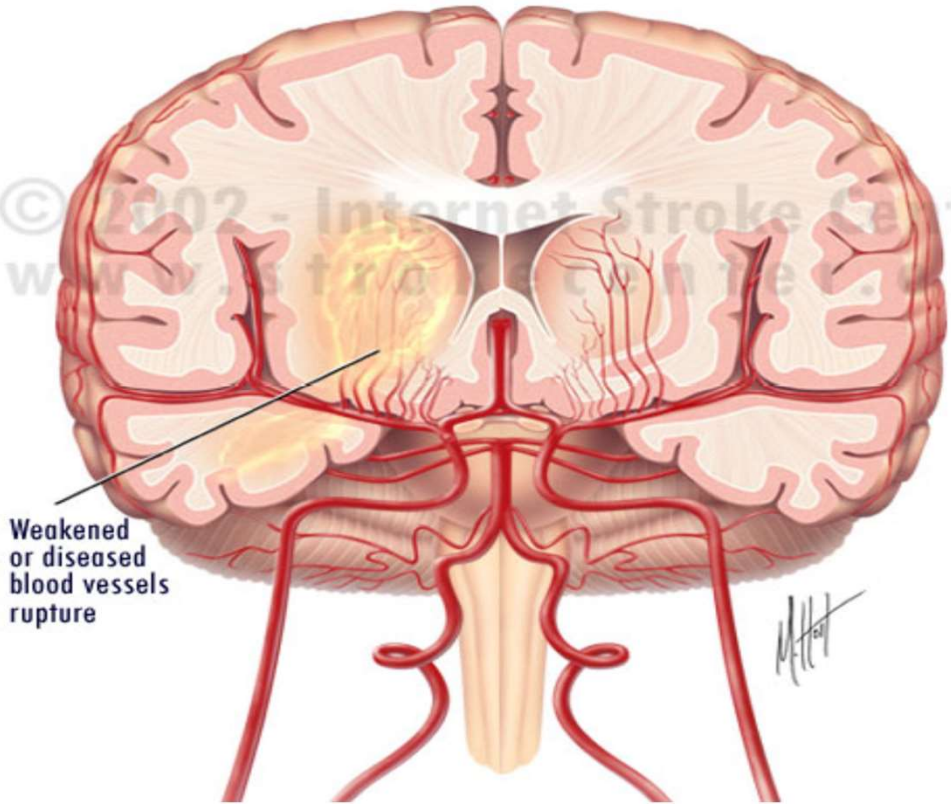
Ischemic Stroke

- Ischemic strokes account for 87% of all strokes and are due either to
  - local thrombus formation or
  - emboli that occlude a cerebral artery.
  - Hypoperfusion
- **Cerebral atherosclerosis** is a causative factor in most cases of ischemic stroke, although 30% are of unknown etiology.
- Emboli can arise either from intra- or extracranial arteries.
  - 20% of embolic strokes arise from the heart.

Hemorrhagic Stroke

- Hemorrhagic strokes account for 13% of strokes and include
  - **Subarachnoid hemorrhage**
    - May result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation.
  - **Intracerebral hemorrhage**
    - Occurs when a ruptured blood vessel within the brain parenchyma causes formation of a hematoma.
  - **Subdural hematomas**
    - Most often caused by trauma

Intracranial Hemorrhage (ICH)

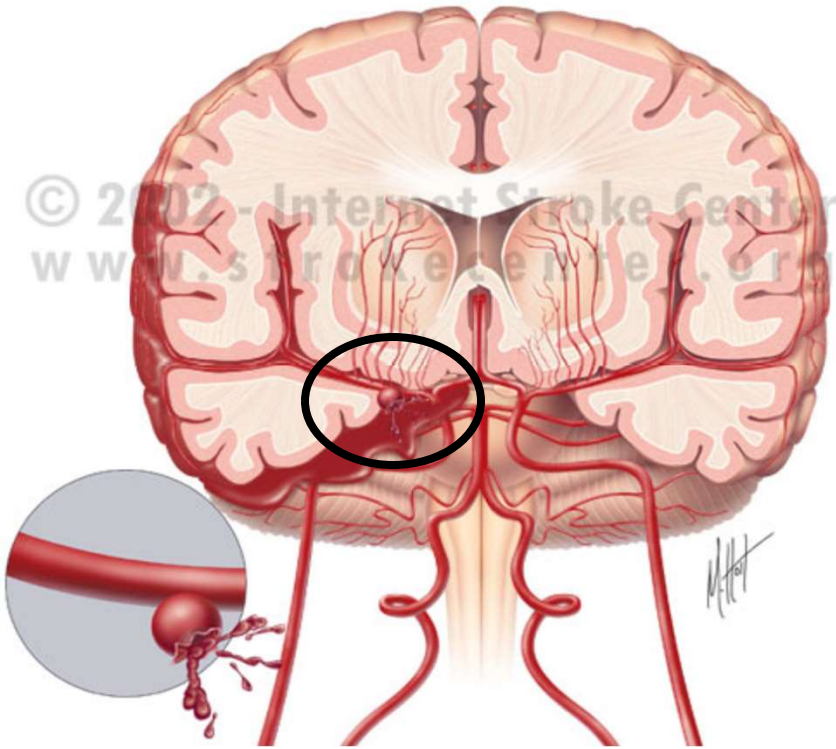


Source: www.strokecenter.org

A spontaneous rupture of an intracranial vessel leading to hemorrhage in brain

Subarachnoid Hemorrhage (SAH)

- Out-pouching of sac caused by weakness of wall
- Arteriovenous malformations (AVM)
- Rupture of intracranial aneurysm



Source: www.strokecenter.org

Clinical Presentations

- Cognitive or language deficits
- Weakness on one side of the body (Hemiparesis)
- Inability to speak (aphasia)
- Loss of vision
- Vertigo
- Falling
- Headache

Diagnosis

- **Laboratory tests**
  - Laboratory tests for hypercoagulable states should be done only when the cause of the stroke cannot be determined.
    - Protein C, protein S, and antithrombin III
    - Antiphospholipid antibodies
- **Imaging Studies**
  - **Computed tomography (CT)** head scan
  - **Magnetic resonance imaging (MRI)**of the head will reveal areas of ischemia with higher resolution and earlier than the CT scan.
  - **Diffusion-weighted imaging** will reveal an evolving infarct within minutes

Desired Outcome

- The goals of treatment for acute stroke are to:
  - Reduce the ongoing neurologic injury and decrease mortality and long-term disability
  - Prevent complications secondary to immobility and neurologic dysfunction
  - Prevent stroke recurrence

Treatment
General Approach

- The initial approach is;
  - To ensure adequate respiratory and cardiac support and
  - To determine quickly whether the lesion is ischemic or hemorrhagic based on a CT or MRI scan.
    - Because treatment differs and fibrinolytic therapy must be avoided until hemorrhagic stroke is ruled out.

- Ischemic stroke patients presenting within hours of symptom onset should be evaluated for **reperfusion therapy.**

- **Blood Pressure Control**
  - Elevated blood pressure should remain untreated in the acute period (first 7 days) after ischemic stroke because of the risk of decreasing cerebral blood flow and worsening symptoms.
  - The pressure should be lowered if it exceeds 220/120 mm Hg or there is evidence of aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy.
  - If blood pressure is treated in the acute phase, short-acting parenteral agents (e.g., labetalol, nicardipine, nitroprusside) are preferred.

Supportive Therapy

IV fluids	- Avoid excessive fluid administration - NS at 50 ml/h
Blood glucose	- Treat hypoglycemia with D50 - Treat hyperglycemia with insulin if Glu > 200mg/dl
Oral intake	- NPO initially until swallowing assessed
Oxygen	- Supplement if indicated (SaO_2 <90%)
Temperature	- Oral or rectal paracetamol as needed (T > 100.4°F)

Inclusion and Exclusion Criteria for Alteplase (rt-PA) Use in Acute Ischemic Stroke

Inclusion Criteria

- 18 years of age or older (> 80 years old relative exclusion for extended treatment time)
- Clinical diagnosis of ischemic stroke causing a measurable neurological deficit
- Time of symptom onset well established to be less than 4.5 hours before treatment would begin

Exclusion Criteria

- Evidence of multilobar infarction on CT scan of the brain (> 1/3 cerebral hemisphere) prior to treatment
- Clinical presentation suggestive of SAH even with a normal head CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to: (a) platelet count less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$); (b) heparin within 48 hours with an elevated aPTT; or (c) current oral anticoagulant use (eg, warfarin) or recent use with an elevated PT (> 15 seconds) or INR (> 1.7)
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)

- Blood glucose concentration < 50 mg/dL (2.8 mmol/L)
- Recent intracranial or intraspinal surgery, significant head trauma, or previous stroke within 3 months
- Recent arterial puncture at a noncompressible site in previous 7 days
- Lumbar puncture within 7 days
- History of previous intracranial hemorrhage
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- SBP > 185 mm Hg or DBP > 110 mm Hg at time of treatment, or patient requires aggressive treatment to reduce BP to within these limits

Relative Exclusion Criteria

- Consider risk to benefit of IV rt-PA if any relative contraindications are present:
  - Only minor or rapidly improving stroke symptoms
  - Pregnancy
  - Witnessed seizure at onset of stroke symptoms with postictal residual neurological impairments
  - Major surgery or serious trauma within 14 days
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Pharmacologic Therapy of Ischemic Stroke

- IV tissue plasminogen activator (alteplase) within 3 hours of onset
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- **Warfarin**
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Pharmacologic Therapy of Hemorrhagic Stroke

- There are currently **no standard pharmacologic strategies** for treating intracerebral hemorrhage.

- The calcium channel blocker **nimodipine**
  - Is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia.
  - No later than 96 hours following SAH.
- Hemostatic Therapy
  - Recombinant factor VIIa has been shown to have a benefit in the treatment of ICH.

Evaluation Of Therapeutic Outcomes

- Patients with acute stroke should be monitored intensely for the development of
  - neurologic worsening
  - Complications and
  - adverse effects from treatments

Pharmacotherapy of Stroke

Definition

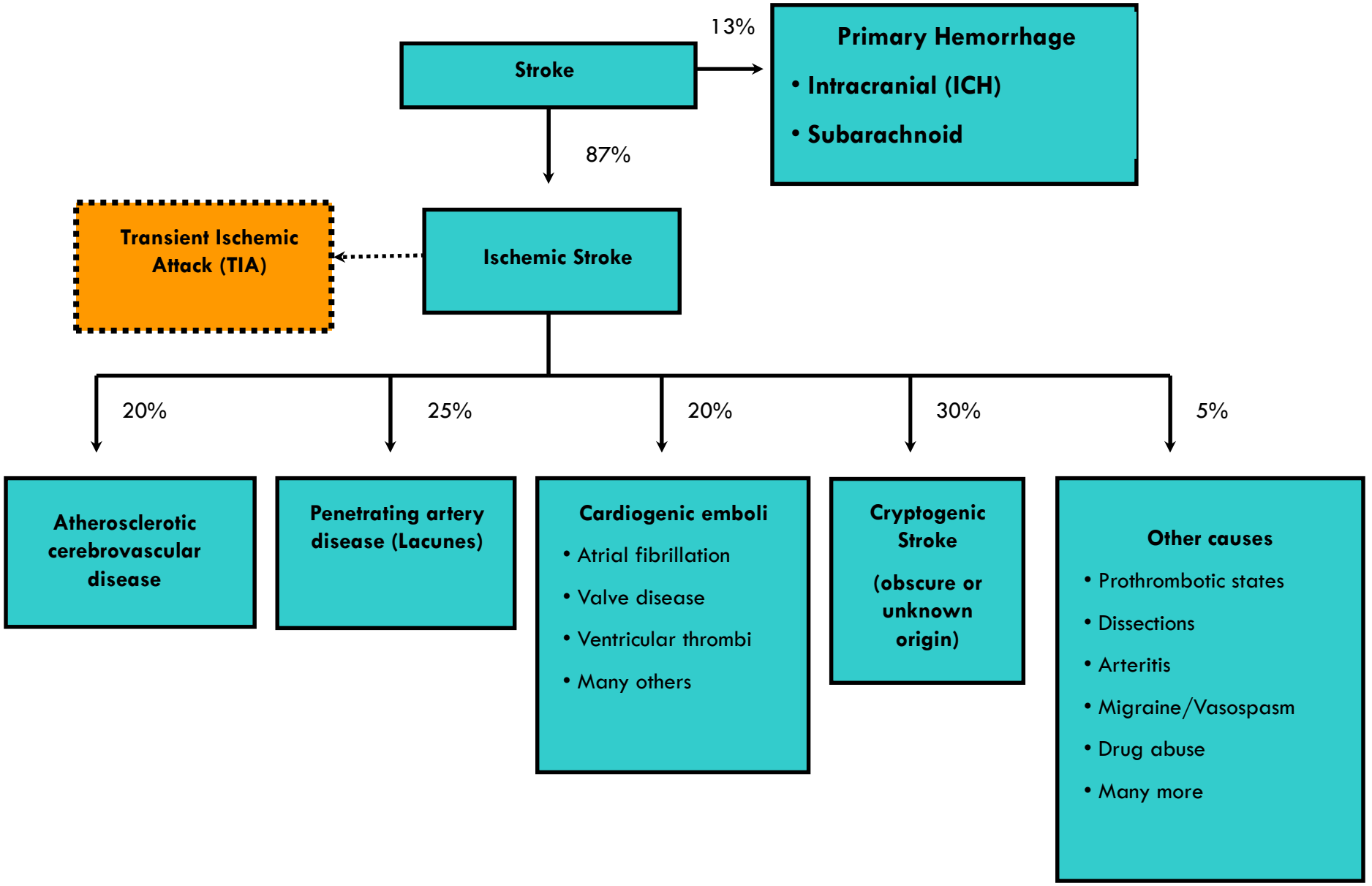
- Stroke is a term used to describe
  - an abrupt onset of focal neurologic deficit that lasts **at least 24 hours** and is presumed to be of **vascular origin**
  - Second leading cause of death next to heart disease
  - Stroke can be either **ischemic** or **hemorrhagic**
    - Diametrically opposite conditions
    - Block in a blood vessel supplying to a part of brain
    - A bleed in the brain
- Transient ischemic attacks (TIAs) are
  - Focal ischemic neurologic deficits lasting **less than 24 hours** and usually less than 30 minutes.

Pathophysiology

Risk Factors For Stroke

- **Non-modifiable risk factors**
  - **Age (> 55 years)**
  - Male gender
  - Race (African American, Asian, Hispanic)
  - Family history of stroke
  - **Low birth weight**
- **Major modifiable risk factors**
  - **Hypertension**
  - **Cardiac disease** (especially atrial fibrillation)
  - **Diabetes mellitus**
  - **OCs(high estrogen content)**
  - **Dyslipidemia**
  - **Lifestyle factors**
    - **Cigarette smoking**
    - **Excessive alcohol use**
    - **Physical inactivity**
    - **Obesity**
    - **Diet**
    - **Cocaine and intravenous drug use**
    - **Low socioeconomic status**

Stroke Classification



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Pharmacotherapy of Venous Thromboembolism (VTE)

Learning Objectives

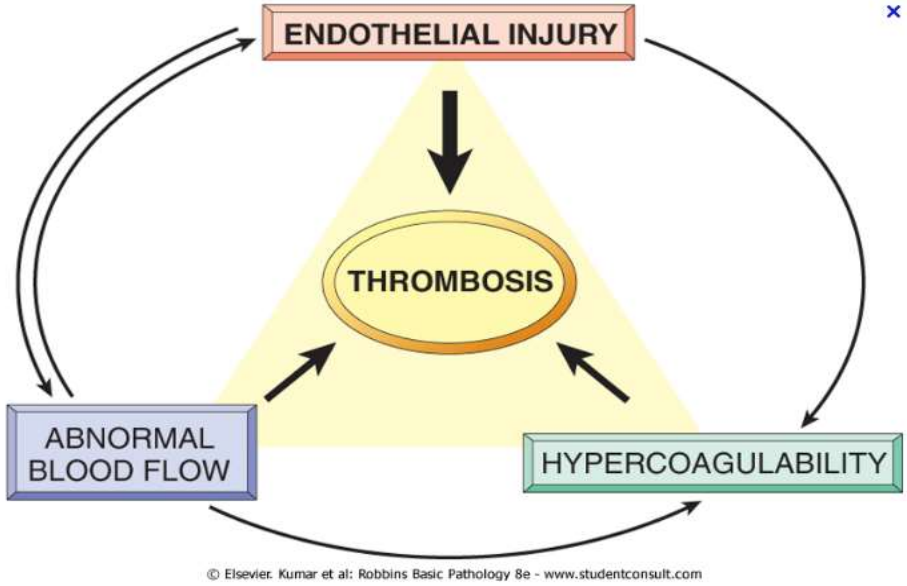
- **At the end, the students will be able to:**
  - Identify risk factors and signs and symptoms of deep vein thrombosis and pulmonary embolism.
  - Determine a patient's relative risk (low, moderate, high, or very high) of developing venous thrombosis.
  - Formulate an appropriate prevention strategy for a patient at risk for deep vein thrombosis.
  - Formulate an appropriate treatment plan for a patient who develops a deep vein thrombosis or pulmonary embolism

Definition

- Potentially fatal disorder and significant health problem in our aging society
- VTE results from **clot formation in the venous circulation** and is manifested as;
  - Deep vein thrombosis (DVT)
    - Blood clot (thrombus) forms in one or more of the deep veins in the body, usually in your legs.
  - Pulmonary embolism (PE)
    - A thrombus that arises from the systemic circulation and **lodges in the pulmonary artery** or one of its branches, causing complete or partial obstruction of pulmonary blood flow.
- Death from PE can occur **within minutes** after the onset of symptoms, before effective treatment can be given.
- But death from DVT is rare.

Risk factors for VTE

- VTE risk factors can be categorized in one of the three elements of Virchow triad:
  - Venous stasis
  - Vascular injury and
  - Hypercoagulability



- In addition
  - Age > 60years
  - History of VTE
  - Heavy smoking > 25 cigs/day
  - Pregnancy
  - Estrogen- containing contraception
  - Heparin Induced thrombocytopenia

- **Venous Stasis**
  - Stasis of blood favors clotting in part through reduced clearance of activated clotting factors from sites of clot formation.
  - Is slowed blood flow in the deep veins of the legs resulting from
    - Damage to venous valves
    - Vessel obstruction
    - Prolonged periods of immobility or
    - Increased blood viscosity
  - Conditions associated with **venous stasis** include
    - Major medical illness (e.g., HF, MI)
    - Major surgery
    - Paralysis (e.g., stroke, spinal cord injury)
    - Polycythemia vera
    - Obesity
    - Varicose veins

- **Vascular Injury**

  – May result from major;

    - Pressure (hypertension
    - Orthopedic surgery (e.g., knee and hip replacement)
    - Trauma (especially fractures of the pelvis, hip or leg)
    - Indwelling venous catheters

- **Hypercoagulable states** include;
  - Malignancy
  - Activated protein C resistance
  - Deficiency of protein C, protein S or antithrombin III
  - Factor VIII or XI excess
  - Antiphospholipid antibodies
  - Estrogens and SERMs have been linked to venous thrombosis,
    - Perhaps due in part to increased serum clotting factor concentrations.

Pathophysiology

- **The coagulation cascade**
  - The arrest of bleeding (essential for life)
  - Stepwise series of enzymatic reactions
  - Triggered either the **intrinsic** or **extrinsic** pathways
  - Meet at a **common point** with the activation of factor X.
  - Factor Va, factor Xa converts prothrombin (II) to thrombin (IIa), which then cleaves fibrinogen, forming fibrin monomers
  - Factor XIII covalently bonds fibrin strands together
  - The fibrinolytic protein **plasmin** ultimately degrades the fibrin mesh into soluble end products

- Majority of thrombi begin in the **lower extremities.**
- Once formed, a venous thrombus may:
  - Remain asymptomatic
  - Lyse spontaneously
  - Obstruct the venous circulation
  - Propagate into more proximal veins
  - Embolize or act in any combination of these ways.
- Even asymptomatic patients may experience long-term consequences, such as the **postthrombotic syndrome** and **recurrent VTE.**

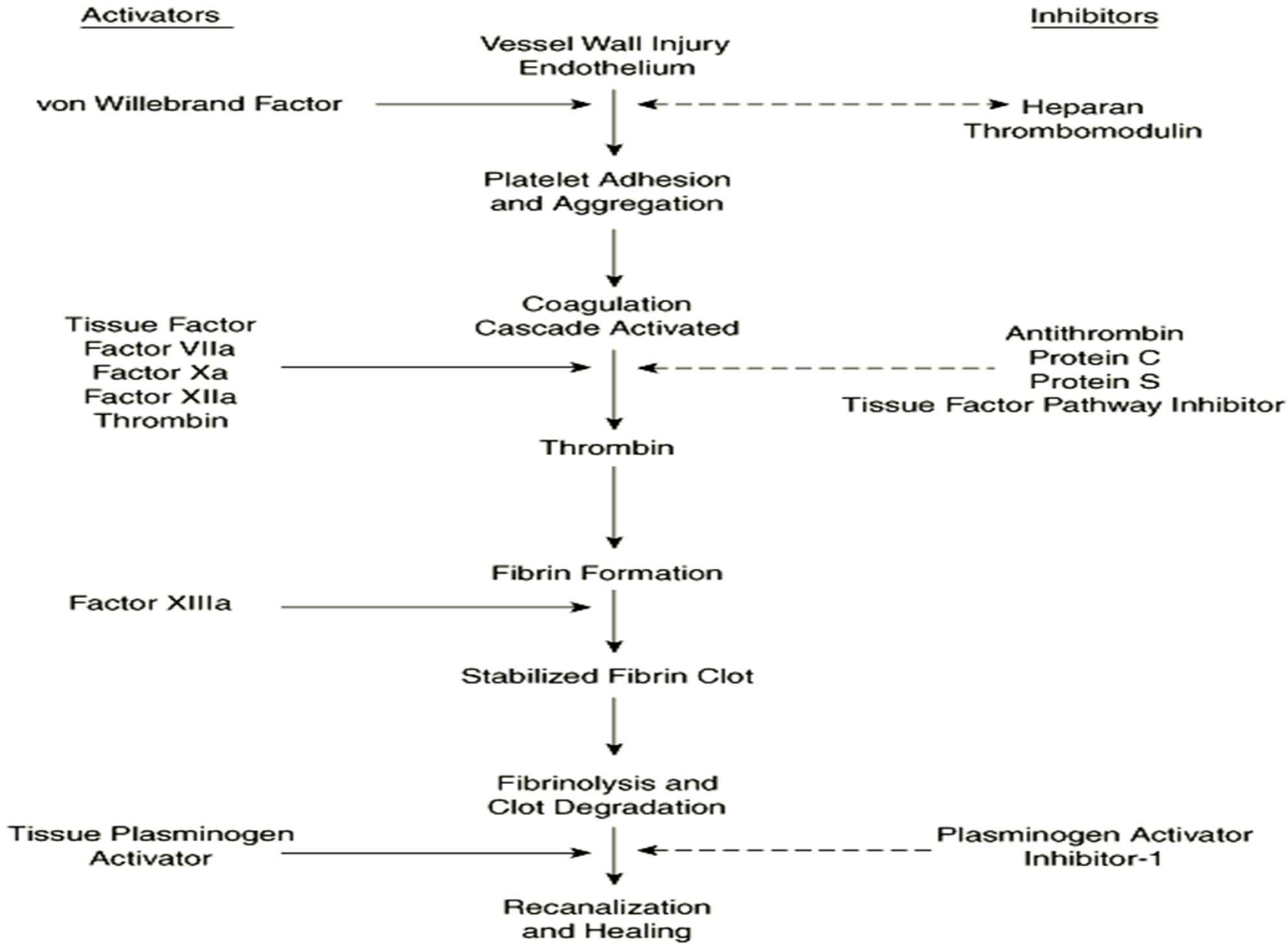
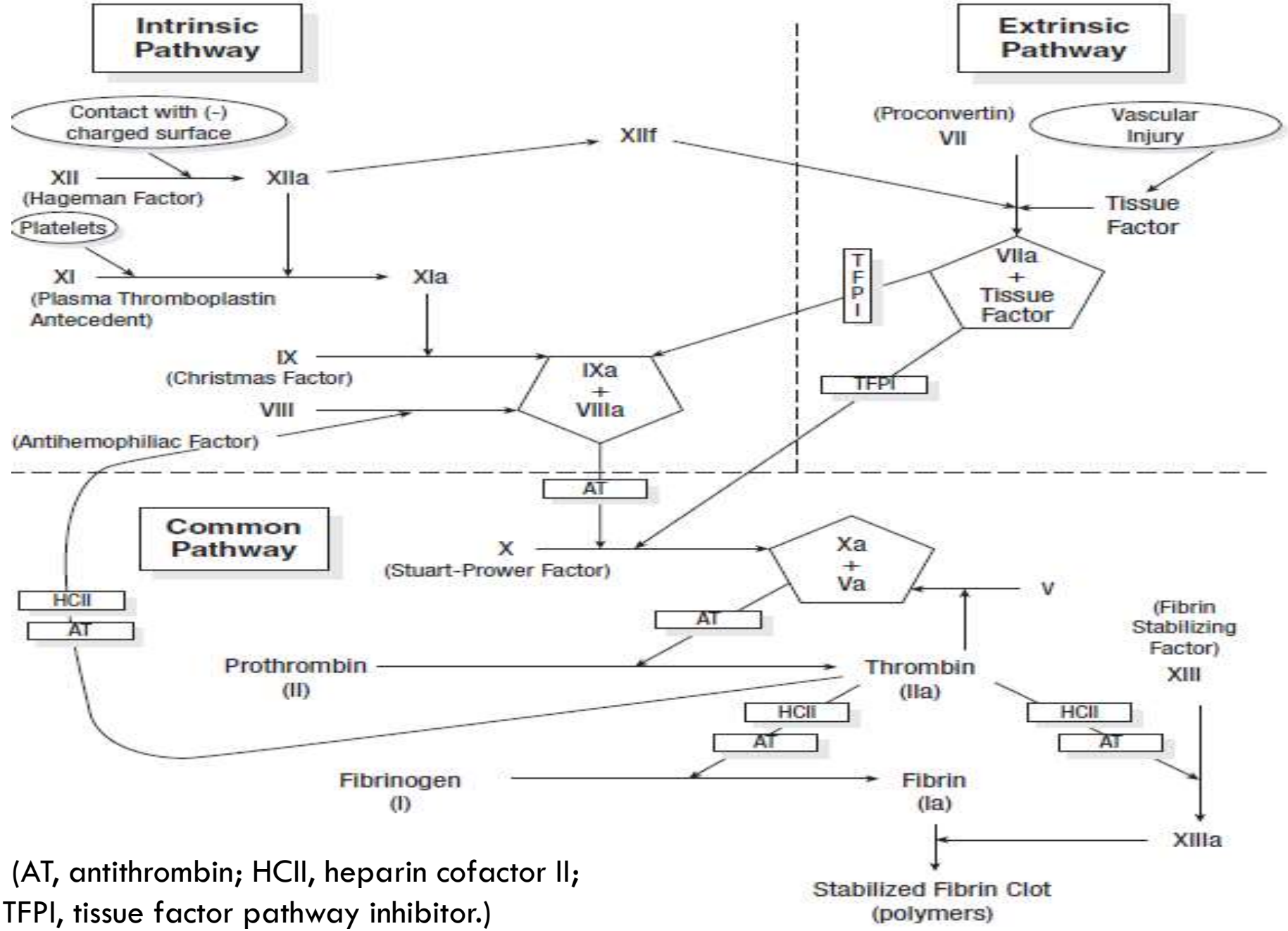

Activators
Inhibitors
Vessel Wall Injury
Endothelium
von Willebrand Factor
Heparan
Thrombomodulin
Platelet Adhesion
and Aggregation
Coagulation
Cascade Activated
Tissue Factor
Factor VIIa
Factor Xa
Factor XIIa
Thrombin
Antithrombin
Protein C
Protein S
Tissue Factor Pathway Inhibitor
Thrombin
Fibrin Formation
Factor XIIIa
Stabilized Fibrin Clot
Fibrinolysis and
Clot Degradation
Tissue Plasminogen
Activator
Plasminogen Activator
Inhibitor-1
Recanalization
and Healing

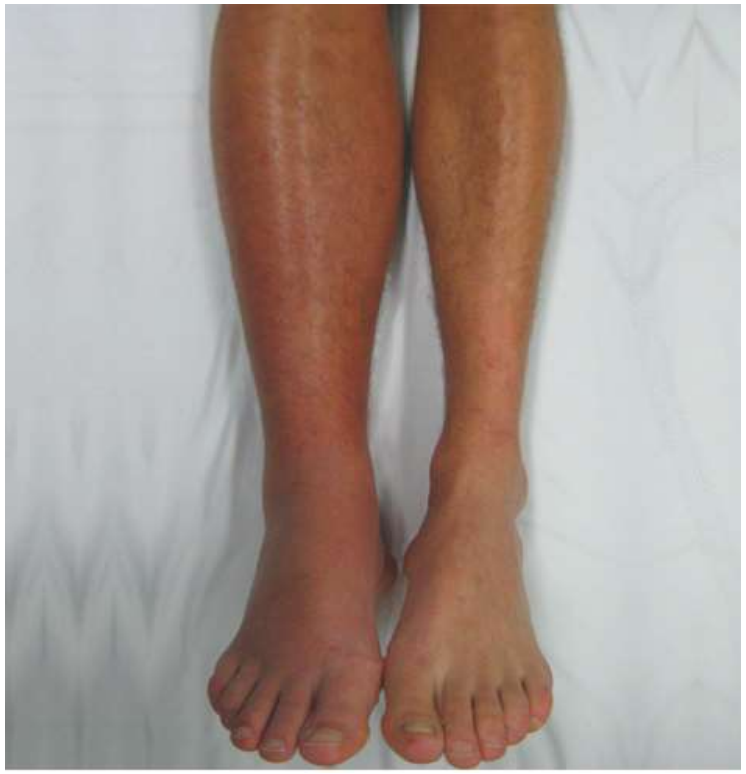
Fig: Coagulation cascade



(AT, antithrombin; HCII, heparin cofactor II; TFPI, tissue factor pathway inhibitor.)

Clinical Presentations

- Up to half patient population with VTE have clinically silent disease
- Symptoms of **DVT** include
  - Unilateral leg swelling
  - Pain, tenderness
  - Erythema and
  - Warmth



- Physical signs may include;
  - **Palpable cord**: The patient's superficial veins may be dilated and a *"palpable cord"* may be felt in the affected leg
  - **Positive Homans' sign:** The patient may experience pain in back of the knee when the examiner dorsiflexes the foot of the affected leg
- **Postthrombotic syndrome** (a long-term complication of DVT caused by damage to venous valves) may produce.
  - Chronic lower extremity swelling, pain, tenderness, skin discoloration and ulceration.
- Symptoms of **PE** include;
  - Dyspnea, tachypnea, pleuritic chest pain, tachycardia, palpitations, cough, diaphoresis, and hemoptysis.
  - Cardiovascular collapse, characterized by cyanosis, shock and oliguria is a life threatening sign.

Diagnosis

- Assessment of the patient's status should focus on the search for **risk factors** e.g.,
  - Increased age
  - Major surgery
  - Previous VTE
  - Trauma
  - Malignancy
  - Hypercoagulable states and
  - Drug therapy
- Signs and symptoms of DVT are **nonspecific**
  - **Objective tests** are required to confirm or exclude the diagnosis.

Laboratory Test

- **D-dimer**
  - Degradation product of fibrin clot
  - Substantially elevated in patients with acute thrombosis
  - Elevated levels can result from a variety of other conditions (**a positive test cannot confirm the diagnosis**)
    - E.g., recent surgery or trauma, pregnancy, increased age and cancer
  - Negative test can help exclude the diagnosis of VTE
    - Very sensitive but not sufficiently specific
- Patients may have an **elevated ESR** and **WBC count.**

Imaging Studies

- **Radiographic contrast studies:** most accurate and reliable
  - **Contrast venography** allows visualization of the entire venous system in the lower extremity and abdomen.
  - **Pulmonary angiography** allows visualization of the pulmonary arteries.

- Because contrast studies are;
  - **Expensive**
  - **Invasive, and**
  - **Technically difficult** to perform and evaluate
- the following noninvasive tests are used frequently for the initial evaluation of patients with suspected VTE
  - **Compression ultrasonography (CUS)** — For DVT
  - **Computed tomography scans**
  - **Ventilation-perfusion scan**

  — For PE

Clinical Assessment Models for Deep Vein Thrombosis and Pulmonary Embolism

Pretest Probability of Deep Vein Thrombosis	
Clinical feature	**Score**
▪ Tenderness along entire deep vein system	1
▪ Swelling of the entire leg	1
▪ Greater than 3 cm difference in calf circumference	1
▪ Pitting edema	1
▪ Collateral superficial veins	1
Risk factors present:	
▪ Active cancer	1
▪ Prolonged immobility or paralysis	1
▪ Recent surgery or major medical illness	1
▪ Alternative diagnosis likely (ruptured Baker cyst, rheumatoid arthritis, superficial thrombophlebitis, or infective cellulitis)	-2
Score ≥3 = high probability; 1–2 = moderate probability; ≤ 0 = low probability	

Pretest Probability of Pulmonary Embolism	
Clinical feature	**Score**
Deep vein thrombosis suspected	
▪ Clinical features of deep vein thrombosis	3
▪ Recent prolonged immobility or surgery	1.5
▪ Active cancer	1
• History of deep vein thrombosis or pulmonary embolism	1.5
▪ **Hemoptysis**	1
▪ Resting heart rate >100 beats/min	1.5
▪ No alternative explanation for acute shortness of breath or chest pain	3
Score ≥6 = high probability; 2–6 = moderate probability; ≤ 1.5 = low probability	

Desired Outcome

- The objectives of treating VTE are
  - To prevent the development of PE and the postthrombotic syndrome
  - To reduce morbidity and mortality from the acute event and
  - To minimize adverse effects and cost of treatment

General Approach to the Prevention of VTE

- Given that VTE is potentially fatal and costly to treat, strategies to prevent DVT in at-risk populations positively impact patient outcomes.
- Relying on the early diagnosis and treatment of VTE is unacceptable because some patients will die before treatment can be initiated.
- Effective prophylaxis can reduce the risk of fatal PE in high-risk surgical and medical populations, whereas early ambulation is often sufficient for those at low risk of VTE.
- Educational programs and clinical decision support systems have been shown to improve the appropriate use of VTE prevention methods.

General Approach to the Treatment of VTE

- Anticoagulation therapies remain the mainstay of tt for VTE.
- Before prescribing a full course of anticoagulation therapy for the tt of VTE.
- It is imperative to establish an accurate diagnosis, thus preventing unnecessary risk of bleeding and expense to the patient
  - Patients with **high probability** of VTE may need parenteral anticoagulation therapy while awaiting the results of diagnostic testing, whereas patients with **intermediate probability** may need parenteral anticoagulation only if diagnostic testing will be delayed more than 4 hours.

- The acute phase of VTE treatment (~7 days) requires rapidly acting anticoagulants such as **unfractionated heparin (UFH), low-molecular-weight heparin (LMWH)**, **fondaparinux**, or **rivaroxaban** to prevent thrombus extension and embolization.
- The early maintenance phase (7 days to 3 months) consists of continued therapeutic anticoagulation aimed at reducing the risk of long-term sequelae.
  - During warfarin initiation injectable anticoagulants should be overlapped with warfarin for at least 5 days and until the patient's international normalized ratio is more than or equal to 2.0 for at least 24 hours.
- Prevent recurrent VTE (long-term anticoagulation therapy extending beyond 3 months).

Unfractionated Heparin (UFH)

- UFH will continue to have a role for acute VTE treatment in patients with creatinine clearance <30 mL/min
- UFH binds to **antithrombin**, provoking a conformational change
  - The UFH-antithrombin complex is 100 to 1,000 times more potent as an anticoagulant than antithrombin alone
  - Antithrombin inhibits the activity of **factors IXa, Xa, XIIa**, and **thrombin (IIa).**
  - **Prevents** the **growth** and **propagation** of a formed thrombus
  - Must be given parenterally, preferably by the **IV** or **subcutaneous** (SC) route.
  - Intramuscular administration is discouraged
  - Because cause large hematomas.

Weight-Based[a] UFH Dosing for Continuous IV Infusion

Indication	Initial Loading Dose	Initial Infusion Rate
DVT/PE	80-100 units/kg Max = 10,000 units	17-20 units/kg/hr Max = 2,300 units/hr
Maintenance Infusion Rate		
AntiXa(U/mL)/aPTT (sec)[b]	**Dose adjustment**	
< 0.15/< 37	80 units/kg bolus, then ↑ infusion by 4 units/kg/hr	
0.15-0.29/37-47	40 units/kg bolus, then ↑ infusion by 2 units/kg/hr	
0.3-0.7/48-71	No change	
0.71-1/72-93	↓ Infusion by 2 units/kg/hr	
> 1/> 93	Hold infusion for 1 hr, then ↓ by 3 units/kg/hr	

[a]Use actual body weight for all calculations. Adjusted body weight may be used for obese patients. [b]aPTT may vary based on individual assays.

- **Adverse Effect**
  - **Bleeding** is the primary associated with UFH.
  - **Protamine sulfate** an antidote during bleeding
  - **Heparin-induced thrombocytopenia (HIT)**
    - A baseline platelet count should be obtained before therapy is initiated and then every-other-day
  - Prolonged use, alopecia, hyperkalemia, and osteoporosis.
- The **activated partial thromboplastin time (aPTT)** should be measured
  - prior to initiation of therapy then no sooner than 6 hours after beginning
  - Once the target aPTT is achieved **daily monitoring**
- **Contraindications** to heparin therapy include;
  - Hypersensitivity to the drug
  - Active bleeding
  - Hemophilia
  - Severe liver disease with elevated prothrombin time (PT)
  - Severe thrombocytopenia
  - Malignant hypertension and
  - Inability to meticulously supervise and monitor treatment

Low-molecular-weight Heparins

- **LMWHs** are fragments of UFH with approximately one-third the molecular weight of UFH.
- Like UFH, the LMWHs
  - Enhance and accelerate the activity of **antithrombin** and prevent the growth and propagation of formed thrombi.
- Advantages of LMWHs over UFH include:
  - More predictable anticoagulation dose response
  - improved SC bioavailability
  - dose-independent clearance
  - longer biologic half-life
  - lower incidence of thrombocytopenia and
  - less need for routine laboratory monitoring

- The peak anticoagulant effect is seen in **3 to 5 hours** after SC dosing.
- The recommended doses (based on actual body weight) for treatment of DVT with or without PE are:
  - **Enoxaparin**
    - 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours
  - **Dalteparin**
    - 100 units/kg every 12 hours or 200 units/kg every 24 hours
  - **Tinzaparin**
    - 175 units/kg every 24 hours

- Data on the use of LMWH in patients with end-stage renal disease receiving hemodialysis are very limited; thus, UFH is preferred for these patients
- For patients with creatinine clearance <30 mL/min (<0.5 mL/s) who require VTE prophylaxis, enoxaparin 30 mg once daily is recommended.
- But dosing recommendations are not available in the setting of renal insufficiency for dalteparin or tinzaparin.

Fondaparinux

- Fondaparinux sodium is a **selective inhibitor of factor Xa.**
- Similar to UFH and the LMWHs, it binds to **antithrombin,** greatly accelerating its activity.
- However, it has no direct effect on thrombin activity at therapeutic plasma concentrations.
- It is approved for
  - Prevention of VTE in patients undergoing orthopedic (hip fracture, hip and knee replacement) surgery and
  - For treatment of VTE

Direct Thrombin Inhibitors

- Drugs: lepirudin, bivalirudin, argatroban, and desirudin
- Interact directly with thrombin and do not require anti-thrombin to have antithrombotic activity.

- They are capable of inhibiting both circulating and clot-bound thrombin, which is a potential advantage over UFH and the LMWHs.

- They also **do not induce immune-mediated thrombocytopenia** and are widely used for the treatment of HIT.

Warfarin

- Most prescribed anticoagulant
- Anticoagulant of choice for long-term/extended anticoagulation
- Requires continuous monitoring & patient education
  - Narrow therapeutic index
  - Many food & drug interactions
- Inhibit synthesis of vit K dependent cloting factors such as pro-thrombin (II); factors VII, IX, and X
- Effect is not achieved for before 6 days after initiation of therapy
- For patients with acute venous thrombosis, UFH, LMWH, or fondaparinux should be overlapped with warfarin therapy for at least **5** days until *the INR is greater than or equal to 2 for at least 24 hours.*
- The usual initial dose is **5 to 10 mg.**
- monitored by the prothrombin time (PT) or international normalized ration (INR) (target: 2 to 3 for DVT or PE)
- Most of the time administered for 3 months
- Patients with unprovoked (idiopathic) VTE have a high recurrence rate and
  - should be considered for **indefinite** oral anticoagulation if possible, but should receive at least 6 to 12 months of therapy.

- **Adverse Effects**
  - **Bleeding risk:** at different site
  - Patients with a mildly elevated INR (3.5 to 5) and no signs or symptoms of bleeding can usually be managed by
  - either reducing the dose or holding one or two warfarin doses.
  - If **rapid reduction of an elevated INR** is required,
  - oral or IV administration of **vitamin K1(phytonadione)** can be given.
- Absolute contraindications to warfarin include
  - active bleeding
  - hemorrhagic tendencies
  - **Pregnancy**
  - a history of warfarin-induced skin necrosis.

Thrombolysis And Thrombectomy

- Thrombolytic agents are proteolytic enzymes
  - That enhance the conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix.
  - Not been shown to improve morbidity or mortality and is associated with a **substantial risk of hemorrhage.**
- For these reasons, thrombolytics should be reserved for patients with PE who are most likely to benefit
  - Those who present with shock
  - Hypotension
  - Right ventricular strain or
  - Massive DVT with limb gangrene
- Three thrombolytic agents and regimens are available for treatment of DVT and/or PE:
- **Streptokinase:**
  - 250,000 units IV over 30 minutes followed by a continuous IV infusion of 100,000 units/hour for 24 hours (PE) or 24 to 72 hours (DVT).
- **Urokinase:**
  - For PE, 4,400 international units/kg IV over 10 minutes followed by 4,400 international units/kg/hour for 12 to 24 hours.
- **Alteplase:**
  - For PE, 100 mg by IV infusion over 2 hours.

Prevention Of VTE

- Non-pharmacologic methods improve venous blood flow by mechanical means and include
  - Early ambulation
  - Electrical stimulation of calf muscles during prolonged surgery
  - Graduated compression stockings (GCS)
  - Intermittent pneumatic compression (IPC) devices and
  - Inferior vena cava filters (IVF)
- The LMWHs and fondaparinux provide superior protection against VTE compared with **low-dose** UFH.
- Warfarin is commonly used for VTE prevention after **orthopedic** surgeries of the lower extremities.
- Prophylaxis should be **continued throughout the period of risk.**

Risk Classification and Consensus Guidelines for Venous Thromboembolism Prevention

Level of Risk	Calf Vein Thrombosis (%)	Symptomatic PE (%)	Fatal PE (%)	Prevention Strategies
Low • Minor surgery, age <40 years, and no clinical risk factors	2	0.2	0.002	Ambulation
Moderate • Major or minor surgery, age 40–60 years, and no clinical risk factors • Major surgery, age <40 years, and no clinic risk factors • Minor surgery, with clinical risk factor(s) • Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), and no clinical risk factors	10–20	1–2	0.1–0.4	UFH 5,000 units SC q 12 h Dalteparin 2,500 units SC q 24 h Enoxaparin 40 mg SC q 24 h Tinzaparin 3,500 units SC q 24 h IPC Graduated compression stockings

Risk Classification and Consensus Guidelines for Venous Thromboembolism Prevention

Level of Risk	Calf Vein Thrombosis (%)	Symptomatic PE (%)	Fatal PE (%)	Prevention Strategies
High • Major surgery, age >60 years, and no clinical risk factors • Major surgery, age 40–60 years, with clinical risk factor(s) • Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), with risk factor(s)	20–40	2–4	0.4–1.0	UFH 5,000 units SC q 8 h Dalteparin 5,000 units SC q 24 h Enoxaparin 40 mg SC q 24 h Fondaparinux 2.5 mg SC q 24 h Tinzaparin 75 units/kg SC q 24 h IPC
Highest • Major lower-extremity orthopedic surgery • Hip fracture • Multiple trauma • Major surgery, age >40 years, and prior history of VTE • Major surgery, age >40 years, and malignancy • Major surgery, age >40 years, and hypercoagulable state • Spinal cord injury or stroke with limb paralysis	40–80	4–10	0.2–5	Adjusted dose UFH SC q 8 h (aPTT >36 s) Dalteparin 5,000 units SC q 24 h Desirudin 15 mg SC q 12 h Enoxaparin 30 mg SC q 12 h Fondaparinux 2.5 mg SC q 24 h Tinzaparin 75 units/kg SC q 24 h Warfarin (INR = 2.0–3.0) IPC with UFH 5,000 units SC

Evaluation of Therapeutic Outcomes

- Patients should be monitored for
  - Resolution of symptoms
  - The development of recurrent thrombosis and
  - Symptoms of the postthrombotic syndrome
  - Adverse effects from the treatments
- Coagulation tests (aPTT, PT, INR) should be performed
  - Prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.

Pharmacotherapy of Peripheral Arterial Disease(PAD)

Learning Objectives

- On completion of this session, the student will be able to:
  - Define peripheral arterial disease (PAD) and risk factor.
  - Describe how the diagnosis of PAD is made.
  - Write goals of therapy in the management of PAD.
  - Provide recommendations for smoking cessation and exercise for PAD patients.

Definition

- PAD is the most common form of peripheral vascular disease
  - Which is a manifestation of progressive narrowing of arteries due to **atherosclerosis.**
- PAD is associated with elevated risk of CVD morbidity and mortality
  - Considered a surrogate marker of subclinical CAD and other vascular territories
- The prevalence of PAD is highly dependent on age,
  - Being infrequent in younger individuals and **common in older individuals**

Pathophysiology

- PAD is most commonly a manifestation of systemic atherosclerosis in which
  - The arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque.

- The major risk factors for the development of atherosclerosis are
  - Older age (greater than 40 years)
  - Cigarette smoking
  - Diabetes mellitus
  - Hypercholesterolemia
  - Hypertension and
  - Hyperhomocysteinemia

Clinical Presentations

- Fewer than 50% of patients with PAD are symptomatic
  - From no symptoms at all (typically early in the disease) to pain and discomfort
- The two most common characteristics of PAD are
  - Intermittent claudication (IC) and
    - Lesions with greater than 50% stenosis
  - Pain at rest in the lower extremities
    - Lesions with greater than 80% stenosis

- **Intermittent Claudication (IC)**
  - **Primary indicator** of PAD.
  - It is described as reproducible fatigue, discomfort, cramping, pain, or numbness in the affected extremities (typically the buttock, thigh or calf) during exercise and is resolved within a few minutes with rest.
- **Resting Pain**
  - Typically occurs **later** in the disease when the blood supply is not adequate to perfuse the extremity (**critical limb ischemia**)
  - This can be felt most often at **night** in the feet (typically the toes or heel) while the patient is lying in bed.

Diagnosis

- A detailed **patient history of symptoms** and atherosclerosis **risk factors** (e.g., smoking, hypertension, hyperlipidemia, and diabetes) can be helpful in the diagnosis of PAD.
- **Non specific signs of decreased blood flow** to the extremities e.g.,
  - Cool skin temperature
  - Thin, brittle shiny skin in the leg and feet
  - Thickened toenails
  - Lack of hair on the calf, feet and/or toes
  - In severe cases, visible sores or ulcers or gangrene that are slow to heal and may even be black in appearance

- Differential diagnosis should rule out conditions that may mimic PAD like,
  - Neurologic conditions (e.g., peripheral neuropathy)
  - Inflammatory conditions (e.g., arthritis)
  - Vascular conditions (e.g., DVT)
- The **ABI (Ankle-Brachial Index)**
  - Is a simple, noninvasive, quantitative test that has been proven to be a **highly sensitive** and **specific** (≥90%) tool in the diagnosis of PAD.
  - For measurement of the ABI,
    - The patient lies in the **supine** position as the SBP is measured at the brachial arteries on both arms and the dorsalis pedis and posterior tibial arteries of the legs with a standard sphygmomanometer and a continuous-wave Doppler device.

- The pressures obtained at the dorsalis pedis and posterior tibial arteries are averaged and divided by the mean measurement taken at the left and right brachial arteries.

- An ABI of 1 is considered normal, while a measurement under 0.9 is consistent with PAD.
  - 0.91-0.99= borderline
  - 0.7 - 0.9 = mild PAD
  - 0.4 - 0.7= moderate disease
  - <0.4 =severe PAD

Imaging Studies

- **Magnetic resonance angiography (MRA) and Computed Tomographic angiography (CTA)**
  - Examine the **presence** and **location** of significant **stenosis** and is a reasonable option for patients who are being considered for surgical **revascularization.**
  - Determine the presence of soft tissue diagnostic information that may be associated with PAD (e.g., aneurysms).

- However, as ABI is a sufficient means of diagnosis,
  - **Arteriography** is not necessary or encouraged

Desired Outcome

- **Treatment goals for PAD include,**
  - Increasing maximal walking distance
  - Increasing duration of pain-free walking
  - Improving control of comorbid conditions contributing to the morbidity of the condition
    - e.g., hypertension, hyperlipidemia, and diabetes
  - Improving overall quality of life and reducing cardiovascular complications and death

Non-pharmacologic Therapy

- **Smoking Cessation**
  - Quantity smoked and the duration can negatively impact disease progression and increase mortality.
- **Exercise**
  - Walking exercise programs for patients with PAD have been proven to result in;
    - An increase in walking duration and distance
    - An increase in pain-free walking and
    - A delayed onset of claudication by **179%.**

- **Surgical Interventions**
  - Various surgical procedures are available for patients
    - With **severe, debilitating claudication** who have attempted, and failed, other means of non-pharmacologic and pharmacologic therapy.
  - Recommendations when
    1. There must be a lack of adequate response to exercise therapy and risk factor modification.
    2. The patient must have severe disability from IC resulting in impairment of daily activities
    3. There must be a thorough evaluation of the risks versus benefits of an invasive intervention

Pharmacologic Therapy

- **Hypertension**
  - No specific class of anti-hypertensive drugs are recommended
  - No specific goal
- **Dyslipidemia**
  - LDL goal: maintained at <100 mg/dL
  - non-HDL levels goal: <130 mg/dL.
- **Diabetes Mellitus**
  - ABI screening for all diabetics older than 50 years
  - Maintain HA-1c level of <7%.

Antiplatelet Drug Therapy

- **Aspirin**
  - Patients with PAD should use ASA (160 to 325 mg/day) or clopidogrel (75 mg/day) when ASA is not tolerated or contraindicated.
  - Aspirin Plus Dipyridamole additional risk reduction
- **Clopidogrel**
  - Although clopidogrel was able to reduce serious vascular events, it is significantly less than the reduction seen with ASA.
  - Current recommendations list clopidogrel as a first-line agent, but only in cases where ASA therapy is either not tolerated or contraindicated.
- **Ticlopidine**
  - Has a "black box" warning from the FDA warning providers that use of this agent can cause **neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura, and aplastic anemia**.

- ***Cilostazol***
  - Antiplatelet and vasodilatory effects mediated by the inhibition of phosphodiesterase III
  - Approved for IC
  - 100 mg twice daily
  - ADRs: heart failure, headache, loose stools or diarrhea
- **Pentoxifylline**
  - Methylxanthine derivative.
  - Decrease blood viscosity by decreasing fibrinogen.
  - Pentoxifylline's role in IC therapy is limited.

Evaluation of Therapeutic Outcomes

- Various measurements
  - Hemoglobin A-1c
  - Total cholesterol, LDL, HDL, and non-HDL cholesterol
  - Blood pressure checks in the clinic and patient home blood pressure monitoring can assess the effectiveness of antihypertensive therapy.
- Repeat exercise treadmill walking testing
- Repeat ABI measurements at each patient visit

Shock

Definition

- Shock refers to conditions manifested by hemodynamic alterations (e.g., hypotension, tachycardia, low cardiac output [CO], & oliguria) caused by;
  - Intravascular volume deficit (hypovolemic shock),
  - Myocardial pump failure (cardiogenic shock), or
  - Peripheral vasodilation (septic, anaphylactic, or neurogenic shock).
- The underlying problem in these situations is inadequate tissue perfusion resulting from circulatory failure.

Pathophysiology

- Shock results in failure of the circulatory system to deliver sufficient oxygen (O_2) to body tissues despite normal or reduced O_2 consumption.
  - General pathophysiologic mechanisms of different forms of shock are similar except for initiating events.
- **Hypovolemic shock** is characterized by acute intravascular volume deficiency due to external losses or internal redistribution of extracellular water.
  - This type of shock can be precipitated by hemorrhage, burns, trauma, surgery, intestinal obstruction, & dehydration from considerable insensible fluid loss, overaggressive loop-diuretic administration, & severe vomiting or diarrhea.
  - Relative hypovolemia leading to hypovolemic shock occurs during significant vasodilation, which accompanies anaphylaxis, sepsis, & neurogenic shock.

Pathophysiology…

- Regardless of the etiology, fall in BP is compensated by an increase in sympathetic outflow, activation of the renin-angiotensin system, & other humoral factors that stimulate peripheral vasoconstriction.
- Compensatory vasoconstriction redistributes blood away from the skin, skeletal muscles, kidneys, & GIT toward vital organs (e.g., heart, brain) in an attempt to maintain oxygenation, nutrition, & organ function.
- Severe metabolic lactic acidosis often develops secondary to tissue ischemia & causes localized vasodilation, which further exacerbates the impaired CV state.

Clinical Presentation

- Patients with hypovolemic shock may present with thirst, anxiousness, weakness, lightheadedness, & dizziness. Patients may also report scanty urine output & dark-yellow-colored urine.
- Hypotension, tachycardia, tachypnea, confusion, & oliguria are common symptoms.
- Myocardial & cerebral ischemia, pulmonary edema (cardiogenic shock), & multisystem organ failure often follow.
- Significant hypotension (SBP<90 mm Hg) with reflex sinus tachycardia (>120bpm) & increased respiratory rate (more than 30 breaths/min) are often observed in hypovolemic patients.
- Clinically, the patient presents with extremities cool to the touch & a thread pulse
- If coronary hypoxia persists, cardiac arrhythmias may occur, which eventually lead to irreversible myocardial pump failure, pulmonary edema, & CV collapse.

Clinical Presentation…

- *In a patient with extensive myocardial damage, chest auscultation may reveal heart sounds consistent with valvular heart disease (regurgitation, outflow obstruction) or significant ventricular dysfunction (S_3).*
- Mental status changes associated with volume depletion may range from subtle fluctuations in mood to agitation to unconsciousness.
- Respiratory alkalosis secondary to hyperventilation is usually observed secondary to CNS stimulation of ventilatory centers as a result of trauma, sepsis, or shock.
- Lung auscultation may reveal crackles (pulmonary edema) or absence of breath sounds (pneumothorax, hemothorax).
- Continued insult to the lungs may result in adult respiratory distress syndrome (ARDS).

Clinical Presentation…

- Kidneys are exquisitely sensitive to changes in perfusion pressures. Moderate alterations can lead to significant changes in GFR. Oliguria, progressing to anuria, occurs because of vasoconstriction of afferent arterioles.
- Skin is often cool, pale, or cyanotic (bluish) due to hypoxemia. Sweating results in a moist, clammy feel.
- Redistribution of blood flow away from the GI tract may cause stress gastritis, gut ischemia, &, in some cases, infarction, resulting in GI bleeding.
- Reduced hepatic blood flow, especially in vasodilatory forms of shock, can alter metabolism of endogenous compounds & drugs.
- Progressive liver damage (shock liver) manifests as elevated serum hepatic transaminases & unconjugated bilirubin. Impaired synthesis of clotting factors may increase PT, INR, & aPTT.

Diagnosis & Monitoring

- Information from noninvasive & invasive monitoring & evaluation of past medical history, clinical presentation, & laboratory findings are key components in establishing the diagnosis as well as in assessing general mechanisms responsible for shock.
- Regardless of the etiology, consistent findings include hypotension (SBP <90 mm Hg), depressed cardiac index (CI <2.2 L/min/m^2), tachycardia (HR>100 beats/min), & low urine output (<20 mL/h).

Diagnosis & Monitoring…

- Noninvasive assessment of BP using the sphygmomanometer & stethoscope may be inaccurate in the shock state.
- Pulmonary artery catheterization using the Swan-Ganz catheter is frequently performed for invasive monitoring of multiple CV parameters.
- A Swan-Ganz catheter can be used to determine central venous pressure (CVP); pulmonary artery pressure; cardiac output; & pulmonary artery occlusive pressure (PAOP), an approximate measure of the left ventricular end-diastolic volume & a major determinant of left ventricular preload.

Diagnosis & Monitoring….

- Cardiac output (2.5 to 3 L/min) & Svo_2 (70% to 75%) may be very low in a patient with extensive myocardial damage.
- Respiratory alkalosis is associated with low partial pressure of O_2 (Pao_2) (25 to 35 mm Hg) & alkaline pH, but normal bicarbonate.
- Circulating Sao_2 can also be measured by an oximeter, which is a noninvasive method that is fairly accurate & useful at the patient's bedside.
- Renal function can be grossly assessed by hourly measurements of urine output, but estimation of creatinine clearance based on isolated serum creatinine values in critically ill patients may yield erroneous results.
- Decreased renal perfusion & aldosterone release result in sodium retention, & thus, low urinary sodium (U_{Na} less than 30 mEq/L).

Treatment

Desired Outcome

- The initial goal is to support oxygen delivery through the circulatory system by assuring effective intravascular plasma volume, optimal oxygen-carrying capacity, & adequate BP while definitive diagnostic & therapeutic strategies are being determined.
- The ultimate goals are to prevent further progression of the disease with subsequent organ damage &, if possible, to reverse organ dysfunction that has already occurred.

Treatment

General Principles

- Supplemental oxygen should be initiated at the earliest signs of shock, beginning with 4 to 6 L/min via nasal cannula or 6 to 10 L/min by face mask.
- Adequate fluid resuscitation to maintain circulating blood volume is essential in managing all forms of shock.
- If fluid challenge does not achieve desired end points, pharmacologic support is necessary with inotropic & vasoactive drugs.

Fluid Resuscitation For Hypovolemic Shock

- Initial fluid resuscitation consists of isotonic crystalloid (0.9% sodium chloride or lactated Ringer's solution), colloid (5% plasmanate or albumin, 6% hetastarch), or whole blood.
- Choice of solution is based on oxygen-carrying capacity (e.g., hemoglobin, hematocrit), cause of hypovolemic shock, accompanying disease states, degree of fluid loss, & required speed of fluid delivery.
- Most clinicians agree that crystalloids should be the initial therapy of circulatory insufficiency. Crystalloids are preferred over colloids as initial therapy for burn patients because they are less likely to cause interstitial fluid accumulation.
- If volume resuscitation is suboptimal following several liters of crystalloid, colloids should be considered.
- Some patients may require blood products to assure maintenance of oxygen-carrying capacity, as well as clotting factors & platelets for blood hemostasis.

Crystalloids

- Crystalloids consist of electrolytes (e.g., Na^+, Cl^-, K^+) in water solutions, with or without dextrose.
- Lactated Ringer's solution may be preferred b/c it is unlikely to cause the hyperchloremic metabolic acidosis seen with infusion of large amounts of normal saline.
- Crystalloids are administered at a rate of 500 to 2000 mL/h, depending on the severity of the deficit, degree of ongoing fluid loss, & tolerance to infusion volume.
  - Usually 2 to 4 L of crystalloid normalizes intravascular volume.
- Advantages of crystalloids include rapidity & ease of administration, compatibility with most drugs, absence of serum sickness, & low cost.
- The primary disadvantage is the large volume necessary to replace or augment intravascular volume.
  - Approximately 4 L of normal saline must be infused to replace 1L of blood loss.
  - In addition, dilution of colloid oncotic pressure leading to pulmonary edema is more likely to follow crystalloid than colloid resuscitation.

Colloids

- Colloids are larger molecular weight solutions (more than 30,000 daltons) that have been recommended for use in conjunction with or as replacements for crystalloid solutions.
- Albumin is a monodisperse colloid because all of its molecules are of the same molecular weight, whereas hetastarch & dextran solutions are polydisperse compounds with molecules of varying molecular weights.
- Colloids are useful because their increased molecular weight corresponds to an increased intravascular retention time (in the absence of increased capillary permeability).
- However, even with intact capillary permeability, the colloid molecules will eventually leak through capillary membranes.

Colloids…

- Albumin 5% & 25% concentrations are available.
- It takes approximately 3 to 4 times as much lactated Ringer's or normal saline solution to yield the same volume expansion as 5% albumin solution.
- However, albumin is much more costly than crystalloid solutions.
- The 5% albumin solution is relatively iso-oncotic, whereas 25% albumin is hyperoncotic & tends to pull fluid into the compartment containing the albumin molecules.
- In general, 5% albumin is used for hypovolemic states.
- The 25% solution should not be used for acute circulatory insufficiency unless diluted with other fluids or unless it is being used in patients with excess total body water but intravascular depletion, as a means of pulling fluid into the intravascular space.

Colloids…

- Hetastarch 6% has comparable plasma expansion to 5% albumin solution but is usually less expensive, which accounts for much of its use.
- Dextran-40, dextran-70, & dextran-75 are available for use as plasma expanders (the number indicates the average molecular weight Ã— 1000). These solutions are not used as often as albumin or hetastarch for plasma expansion, possibly due to concerns related to aggravation of bleeding (i.e., anticoagulant actions related to inhibiting stasis of microcirculation) & anaphylaxis, which is more likely to occur with the higher molecular weight solutions.

Colloids…

- The advantage of colloids is their prolonged intravascular retention time compared to crystalloid solutions. In contrast to isotonic crystalloid solutions, which have substantial interstitial distribution within minutes of IV administration, colloids remain in the intravascular space for hours or days depending on factors such as capillary permeability.
- However, colloids (especially albumin) are expensive solutions, & a large study involving almost 7000 critically ill patients found no significant difference in 28-day mortality between patients resuscitated with either normal saline or 4% albumin. For these reasons, crystalloids should be considered first-line therapy in patients with hypovolemic shock.
- Adverse effects of colloids are generally extensions of their pharmacologic activity (e.g., fluid overload, dilutional coagulopathy). Albumin & dextran may be associated with anaphylactoid reactions or anaphylaxis. Bleeding may occur in certain patients receiving hetastarch & dextran.

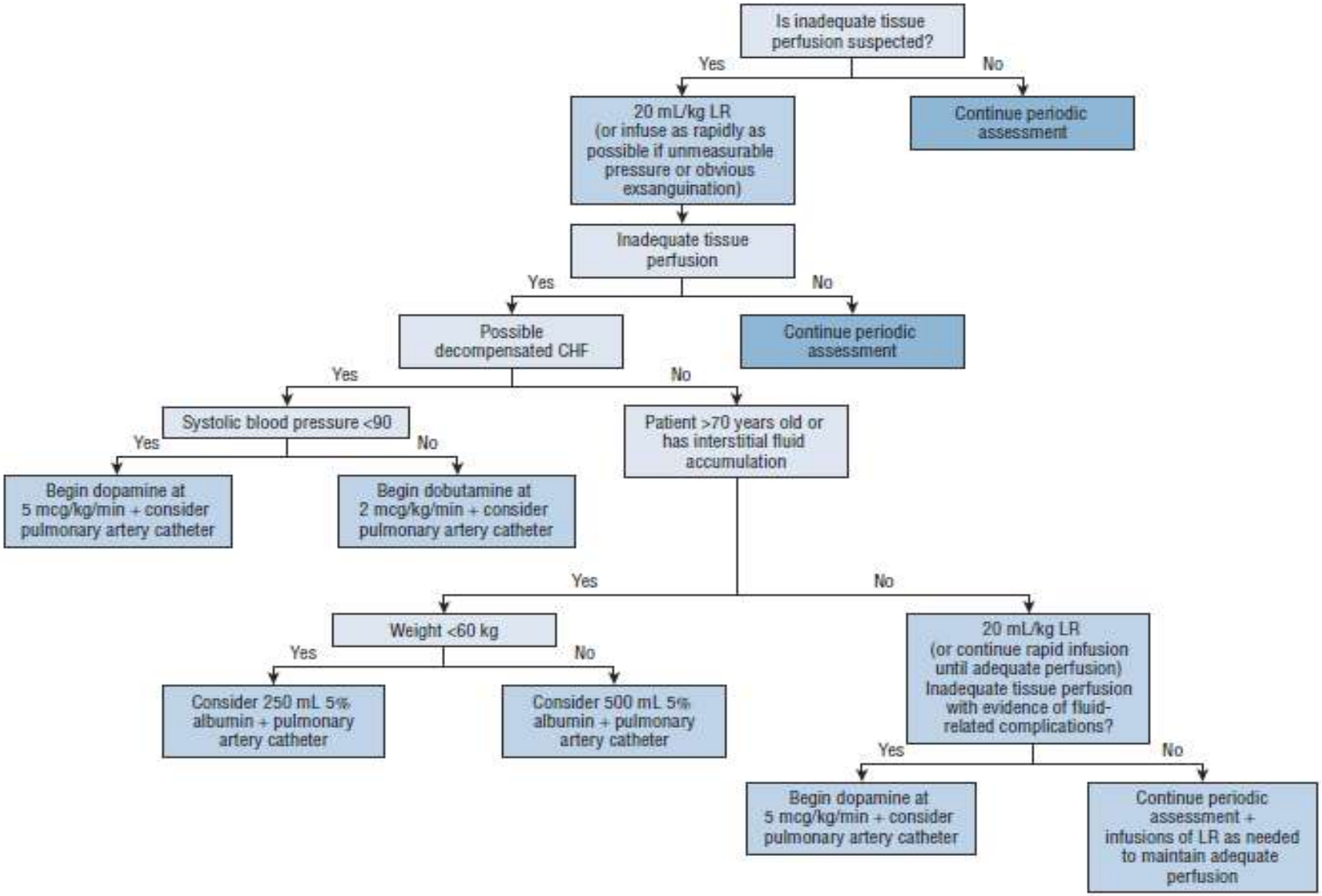
Blood Products

- Whole blood could be used for large volume blood loss, but most institutions use component therapy, with crystalloids or colloids used for plasma expansion.
- Packed red blood cells contain hemoglobin that increases the oxygen-carrying capacity of blood, thereby increasing oxygen delivery to tissues.
- Packed red cells are usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination. The product needs to be warmed before administration, especially when used in children.
- Fresh frozen plasma replaces clotting factors. Although it is often overused, the product is indicated if there is ongoing hemorrhage in patients with a PT or aPTT greater than 1.5 times normal, severe hepatic disease, or other bleeding disorders.
- Platelets are used for bleeding due to severe thrombocytopenia (platelet counts less than 10,000/mm^3) or in patients with rapidly dropping platelet counts, as seen in massive bleeding.
- Cryoprecipitate & Factor VIII are generally not indicated in acute hemorrhage but may be used once specific deficiencies have been identified.
- Risks associated with infusion of blood products include transfusion-related reactions, virus transmission (rare), hypocalcemia resulting from added citrate, elevations in serum potassium & phosphorus concentrations from use of stored blood that has hemolyzed, increased blood viscosity from supranormal hematocrit elevations, & hypothermia from failure to appropriately warm solutions before administration.

Pharmacologic Therapy For Shock

- ***Hypovolemic Shock:*** Inotropic agents & vasopressors are generally not indicated in the initial treatment of hypovolemic shock (assuming that fluid therapy is adequate), as the body's normal response is to increase cardiac output & constrict blood vessels to maintain BP.
- However, once the cause of circulatory insufficiency has been stopped or treated & fluids have been optimized, medications may be needed in patients who continue to have signs & symptoms of inadequate tissue perfusion.
- Pressor agents such as norepinephrine & high-dose dopamine should be avoided if possible because they may increase BP at the expense of peripheral tissue ischemia. In patients with unstable BP despite massive fluid replacement & increasing interstitial fluid accumulation, inotropic agents such as dobutamine are preferred if BP is adequate (SBP 90 mm Hg or greater) because they should not aggravate the existing vasoconstriction. When pressure cannot be maintained with inotropes, or when inotropes with vasodilatory properties cannot be used due to concerns about inadequate BP, pressors may be required as a last resort.

Hypovolemia Protocol For Adults



Vasopressors and inotropes…

- The choice of vasopressor or inotropic agent in septic shock should be made according to the needs of the patient. The traditional approach is to start with dopamine, then norepinephrine; dobutamine is added for low cardiac output states, & occasionally epinephrine & phenylephrine are used when necessary.
  - However, recent observations of improved outcomes with norepinephrine & decreased regional perfusion with dopamine are calling into question the use of dopamine as a first-line agent.
- In general, these drugs act rapidly with short durations of action & are given as continuous infusions. Potent vasoconstrictors such as norepinephrine & phenylephrine should be given through central veins due to the possibility of extravasation & tissue damage with peripheral administration.

- Septic shock:
- Initial hemodynamic therapy for septic shock is administration of IV fluid (30 mL/kg of crystalloid), with the goal of attaining CVP 8 to 12 mm Hg or 15 mm Hg in mechanically ventilated patients or patients with abdominal distention or preexisting ventricular dysfunction.
- Crystalloids are preferred over colloids unless patients are at risk for adverse events from redistribution of IV fluids to extravascular tissues or are fluid restricted.

✓ Norepinephrine is the preferred initial vasopressor in septic shock not responding to fluid administration.

✓ Epinephrine may be added in cases where there is suboptimal hemodynamic response to norepinephrine.

✓ Phenylephrine may be tried as the initial vasopressor in cases of severe Tachydysrhythmias.

Algorithmic approach to resuscitative management of septic shock

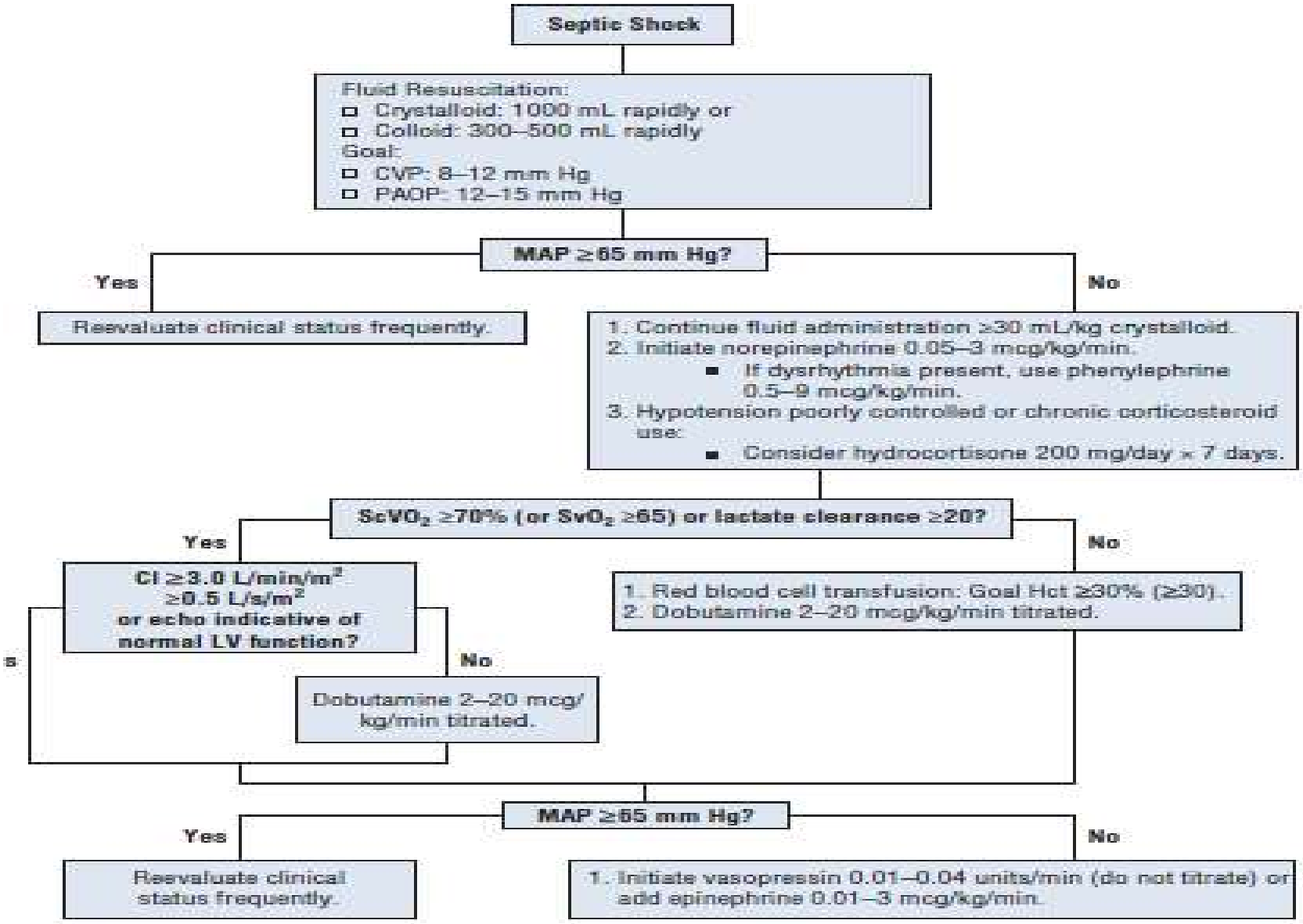


TABLE 12–2 Receptor Pharmacology of Selected Inotropic and Vasopressor Agents Used in Septic Shock[a]

Agent	α_1	α_2	β_1	β_2	D
Dobutamine (0.5–4 mg/mL D_5W or NS)					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	++++	+++	0
Dopamine (0.8–3.2 mg/mL D_5W or NS)					
1–3 mcg/kg/min	0	0	+	0	++++
3–10 mcg/kg/min	0/+	0	++++	++	++++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine (0.008–0.016 mg/mL D_5W or NS)					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0
>0.05–3 mcg/kg/min	++++	++++	+++	+	0
Norepinephrine (0.016–0.064 mg/mL D_5W)					
0.02–3 mcg/kg/min	+++	+++	+++	+/++	0
Phenylephrine (0.1–0.4 mg/mL D_5W or NS)					
0.5–9 mcg/kg/min	+++	+	+	0	0
Vasopressin (0.8 units/mL D_5W or NS)					
0.01–0.04 units/min	0	0	0	0	0

D, dopamine; D_5W, dextrose 5% in water; NS, normal saline.
[a]Activity ranges from no activity (0) to maximal (++++) activity.

- **Dobutamine is used in low CO states despite adequate fluid resuscitation** pressures.

✓ **Vasopressin may be considered as adjunctive therapy in patients who are refractory** to catecholamine vasopressors despite adequate fluid resuscitation.

- Dosage titration & monitoring of vasopressor & inotropic therapy should be guided by clinical response, the goals of early goal-directed therapy, & lactate clearance.
- Vasopressor/inotrope therapy is continued until myocardial depression & vascular hyporesponsiveness (i.e., blood pressure) of septic shock improve, usually measured in hours to days. Discontinuation of therapy should be executed slowly with careful monitoring.

- **Norepinephrine** is first-line therapy for septic shock because it effectively increases MAP. It has strong α1-agonist activity & less potent β1-agonist effects while maintaining weak vasodilatory effects of β2-receptor stimulation.
- Norepinephrine infusions are initiated at 0.05 to 0.1 mcg/kg/min & rapidly titrated to preset goals of MAP (usually at least 65 mm Hg), improvement in peripheral perfusion (to restore urine production or decrease blood lactate), &/or achievement of desired oxygen transport variables while not compromising cardiac index.
- Norepinephrine 0.01 to 2 mcg/kg/min improves hemodynamic parameters to "normal" values in most patients with septic shock.
- As with other vasopressors, norepinephrine dosages exceeding those recommended by most references frequently are needed in critically ill patients with septic shock to achieve predetermined goals.

- **Phenylephrine** is a pure α1-agonist; in sepsis, it improves MAP by increasing cardiac index through enhanced venous return to the heart (increase in CVP & stroke index) & by acting as a positive inotrope.
- Phenylephrine 0.5 to 9 mcg/kg/min, used alone or in combination with dobutamine or low doses of dopamine, improves blood pressure & myocardial performance in fluid-resuscitated septic patients.
- Tachydysrhythmias are infrequent particularly when it is used as a single agent or at higher doses.
- Phenylephrine may be a useful alternative in patients who cannot tolerate tachycardia or tachydysrhythmias from dopamine or norepinephrine & in patients who are refractory to dopamine or norepinephrine.

- **Epinephrine** has combined α- & β-agonist effects; it is an acceptable choice for hemodynamic support of septic shock because of its combined vasoconstrictor & inotropic effects.
- As a result, it is considered an alternative agent.
- Infusion rates of 0.04 to 1 mcg/kg/min alone increase hemodynamic & oxygen-transport variables to supranormal values without adverse effects in septic patients without coronary artery disease.
- Large dosages (0.5–3 mcg/ kg/min) often are required.
- Smaller dosages (0.10–0.50 mcg/kg/min) are effective when epinephrine is added to other vasopressors & inotropes.

- **Dopamine** is generally not as effective as norepinephrine & epinephrine for achieving goal MAP in patients with septic shock.
- Dopamine doses of 5 to 10 mcg/kg/min increase cardiac index by improving contractility & heart rate, primarily from its β1 effects.
- It increases MAP & SVR as a result of both increased CO &, at higher doses (>10 mcg/kg/min), its α1 agonist effects. The clinical utility of dopamine is limited because large dosages are frequently necessary to maintain CO & MAP.
- At dosages exceeding 20 mcg/kg/min, further improvement in cardiac performance & regional hemodynamics is limited. Its clinical use frequently is hampered by tachycardia & tachydysrhythmias, which may lead to myocardial ischemia.
- Use dopamine with caution in patients with elevated preload because it may worsen pulmonary edema.

- **Dobutamine** is an inotrope with vasodilatory properties (an "inodilator"). It is used to increase the cardiac index, typically by 25% to 50%.
- Dobutamine should be started at dosages ranging from 2.5 to 5 mcg/kg/min. Although a dose response may be seen, dosages greater than 5 mcg/kg/min may provide limited beneficial effects on oxygen transport values & hemodynamics & may increase adverse cardiac effects.
- If given to patients who are intravascularly depleted, dobutamine will result in hypotension & a reflexive tachycardia.

- **Vasopressin** produces rapid & sustained improvement in hemodynamic parameters at dosages not exceeding 0.04 units/min.
- Use vasopressin only if response to one or two adrenergic agents is inadequate or as a method for reducing the dosage of those therapies.
- Increased arterial pressure should be evident within the first hour of vasopressin therapy, at which time the dose(s) of adrenergic agent(s) should be reduced while maintaining goal MAP.
- Attempt to discontinue vasopressin when the dosage(s) of adrenergic agent(s) has been minimized (dopamine ≤5 mcg/kg/min, norepinephrine ≤0.1 mcg/kg/min, phenylephrine ≤1 mcg/kg/min, epinephrine ≤0.15 mcg/kg/min).

- **Corticosteroids** can be initiated in septic shock when adrenal insufficiency is suspected, when vasopressor dosages are escalating, or when weaning of vasopressor therapy proves futile.
- Adverse events are few because corticosteroids are administered for a short time, usually 7 days.
- Acutely, elevated BUN, white blood cell count, & glucose may occur.
- In general, treatment of septic shock with corticosteroids improves hemodynamic variables & lowers catecholamine vasopressor dosages with minimal to no adverse effect on patient safety.

Evaluation Of Therapeutic Outcomes

- Monitor patients with suspected volume depletion initially by vital signs, urine output, mental status, & physical examination.
- Electrolytes & renal function tests (BUN & serum creatinine); CBC to assess possible infection, O2-carrying capacity of the blood, & ongoing bleeding; PT & aPTT to assess clotting ability; & lactate concentration & base deficit to detect inadequate tissue perfusion
- Successful fluid resuscitation should increase SBP (>90 mm Hg), CI (>2.2 L/min/ m2), & urine output (0.5–1 mL/kg/h) while decreasing SVR to the normal range.
- MAP of greater than 65 mm Hg should be achieved to ensure adequate cerebral & coronary perfusion pressure.
- Intravascular volume overload is characterized by high filling pressures (CVP >12–15 mm Hg, PAOP >20–24 mm Hg) & ↓sed CO (<3.5 L/min).
- If volume overload occurs, administer furosemide, 20 to 40 mg, by slow IV push to produce rapid diuresis of intravascular volume & “unload” the heart through venous dilation.