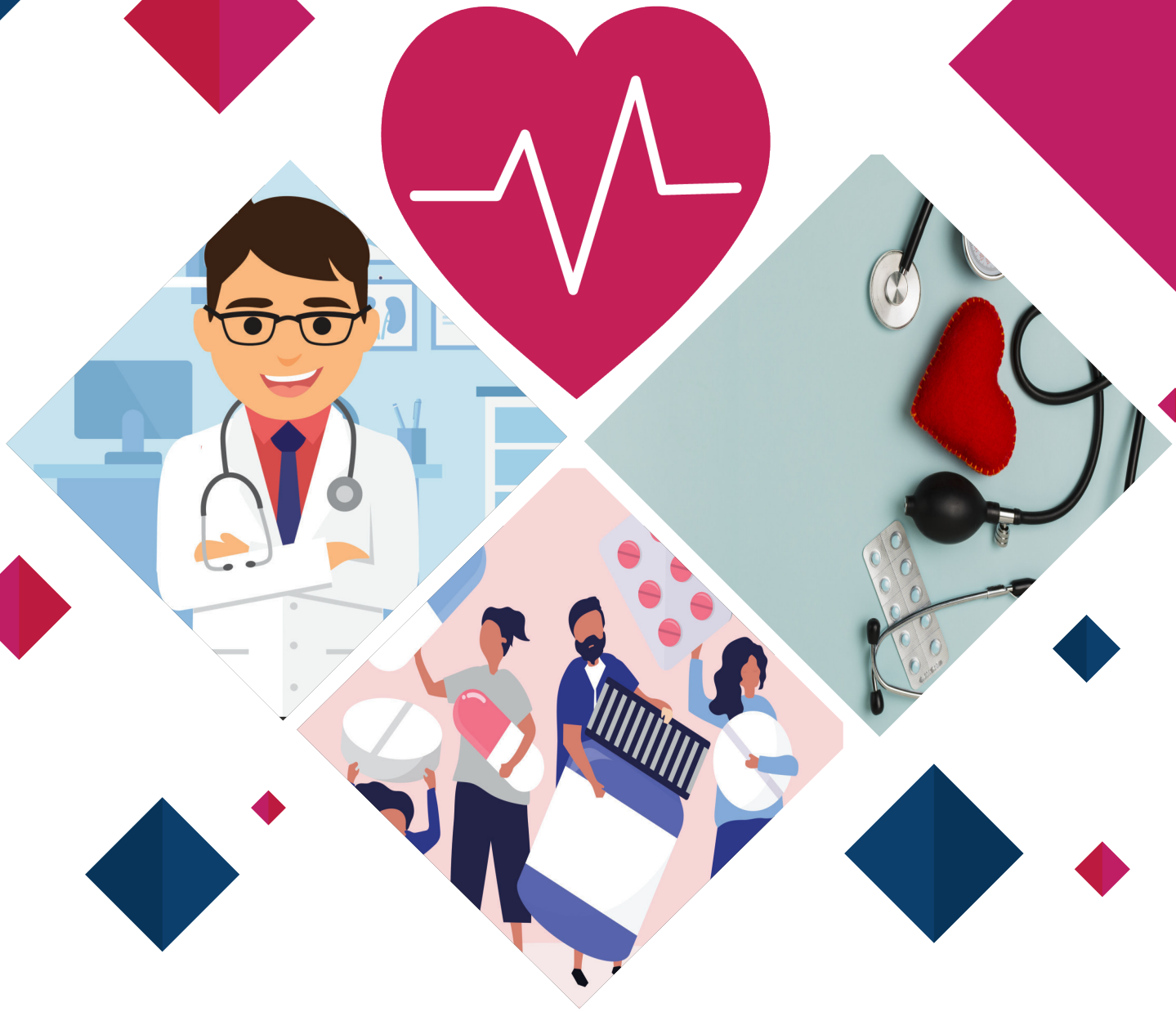
CLINICAL PHARMACY

FOR THIRD YEAR STUDENTS



CLINICAL PHARMACY DEPARTMENT
2019/ 2020

Clinical Pharmacy

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Course Outlines

- Introduction, Clinical Pharmacy services & activities
- SOAP
- Hypertension
- Heart failure
- Dyslipidemia
- Acute coronary syndromes
- Infective endocarditis
- Arrhythmia
- Fluid & electrolyte Imbalance
- Hypovolemic shock
- Anemia
- Coagulation disorders

Lecture Outlines

- Clinical Pharmacy Overview
- SOAP Note
- Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care
- Severity rating of the drug interactions
- Practical Cases

Rational Use of Medicines

- **First, Do No Harm: When Patients Suffer**

- **"Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" WHO.**

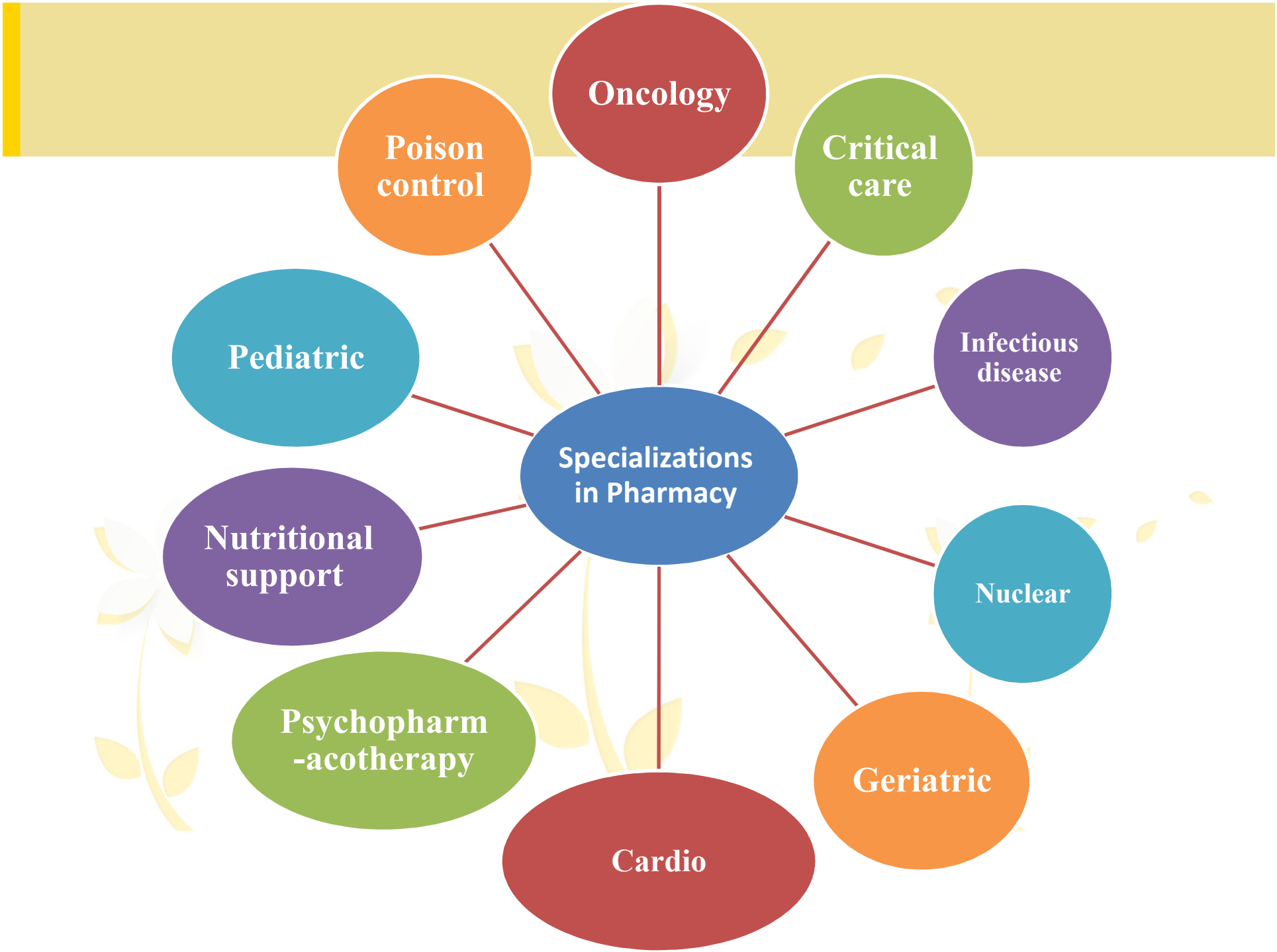
The five rights for correct drug administration:

- Right Patient
- Right Drug
- Right Dose
- Right Route
- Right Time

History of Clinical Pharmacy

- Its development began in the early 1950s, primarily as a result of the efforts of Harry Gold.
- The clinical pharmacy movement began at the University of Michigan in the early 1960s, but much of the pioneering work was done by David Burkholder, Paul Parker, and Charles Walton at the University of Kentucky in the latter part of the 1960s.
- Teaching clinical Pharmacy in Egypt began in Faculty of Pharmacy Tanta University


Community
Consulting
Hospital
Types of Pharmacies
Ambulatory
Clinical
Veterinary
Compounding


Specializations in Pharmacy
Oncology
Poison control
Critical care
Pediatric
Infectious disease
Nutritional support
Nuclear
Psychopharm -acotherapy
Geriatric
Cardio

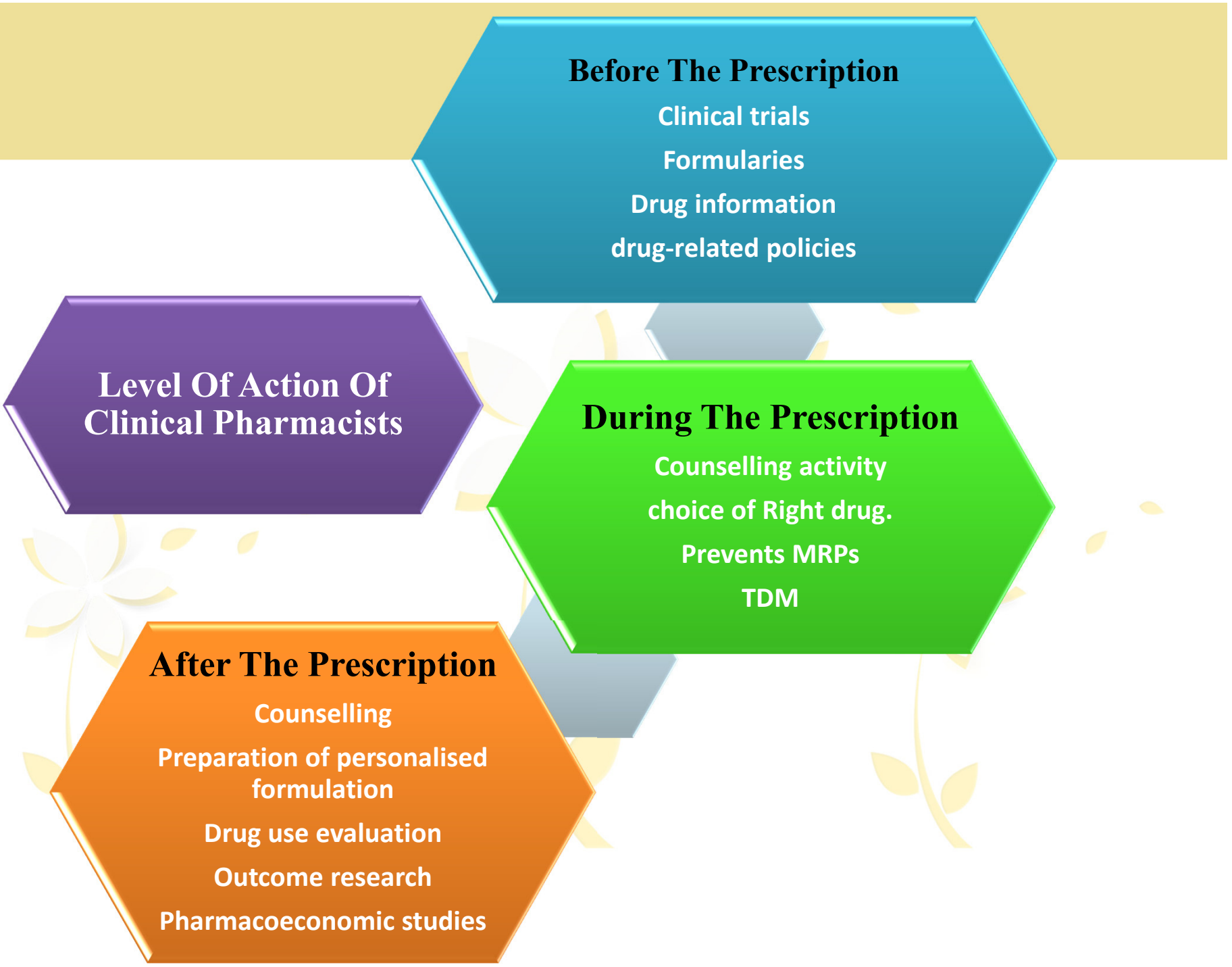
Clinical Pharmacy Definition

- Clinical Pharmacy is a new-born discipline in hospital pharmacy.
- Clinical pharmacy is defined as that area of pharmacy concerned with the science and practice of rational medication use.
- "The active participation of pharmacists in patient health care by giving advice on therapy and monitoring the drug therapy for patient".
- It the area of pharmacy practices that ensure effective, safe & economical use of drugs in patients through the application of specialized skills, knowledge, and functions in patients care.


Minimising the expenditures for pharmacological treatments.
Goals
Minimising the risk of treatment-induced adverse events
Maximising the clinical effect of medicines


Clinical Pharmacy Requirements
Knowledge of drug therapy
Knowledge of nondrug therapy
Knowledge of laboratory and diagnostic skills
Therapeutic planning skills
Patient monitoring skills
Drug Information Skills
Knowledge of the disease
Physical assessment skills
Communication skills


Functions of clinical pharmacist
Selection of drugs
Consulting
Drug information
Teaching & Training
Medication Review
Pharmacoeconomy
Attending Rounds
Clinical Trials
Drug use studies and research
Pharmacokinetics/ therapeutic drug monitoring


Before The Prescription
Clinical trials
Formularies
Drug information
drug-related policies
Level Of Action Of Clinical Pharmacists
During The Prescription
Counselling activity
choice of Right drug.
Prevents MRPs
TDM
After The Prescription
Counselling
Preparation of personalised formulation
Drug use evaluation
Outcome research
Pharmacoeconomic studies

Rational for the pharmacist participation in medical rounds

- Direct patients observations
- Evaluate laboratory results
- Pharmacist input can improve the appropriateness of medications for patients & optimization of medication use.
- More patients were detected with DRPs in the intervention group
- Higher number of drug related problems (DRPs) was prevented and resolved.
- Improved quality of drug use with potential clinical benefits for patients, potential cost savings and costs avoidance for the hospital and pharmacy department.

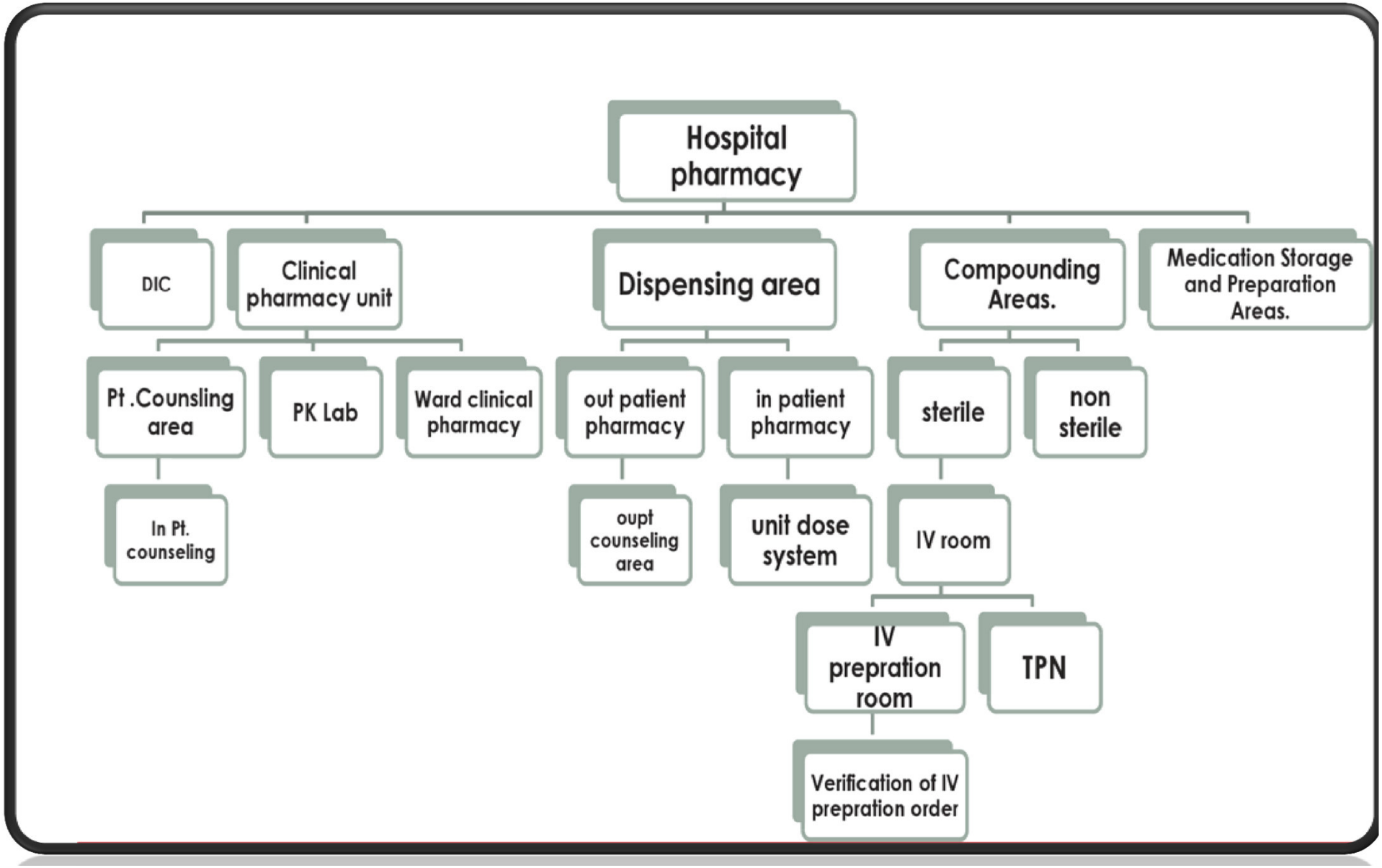
Medication-related problems (MRPs) / (DRPs)

- Unnecessary drug therapy
- Wrong drug
- Dose too low
- Dose too high
- Adverse drug reaction and drug – drug interaction
- Needs for Additional Drug Therapy
- Inappropriate adherence (medication taking behavior).

Problems in implementing pharmaceutical service

- The nature of pharmacy education
- Stagnated leadership
- Legislations: policy and procedures.
- Cost of establishing the service.
- Lack of job satisfaction (low salaries & lack of promotion opportunities).

Organisation chart of Pharmacy department



Approach to and Assessment of Patient Therapy

Problem oriented medical record (POMR)

Guide to Writing SOAP Notes

SOAP Notes

- **Each medical problem is identified, listed sequentially, and assigned a number.**

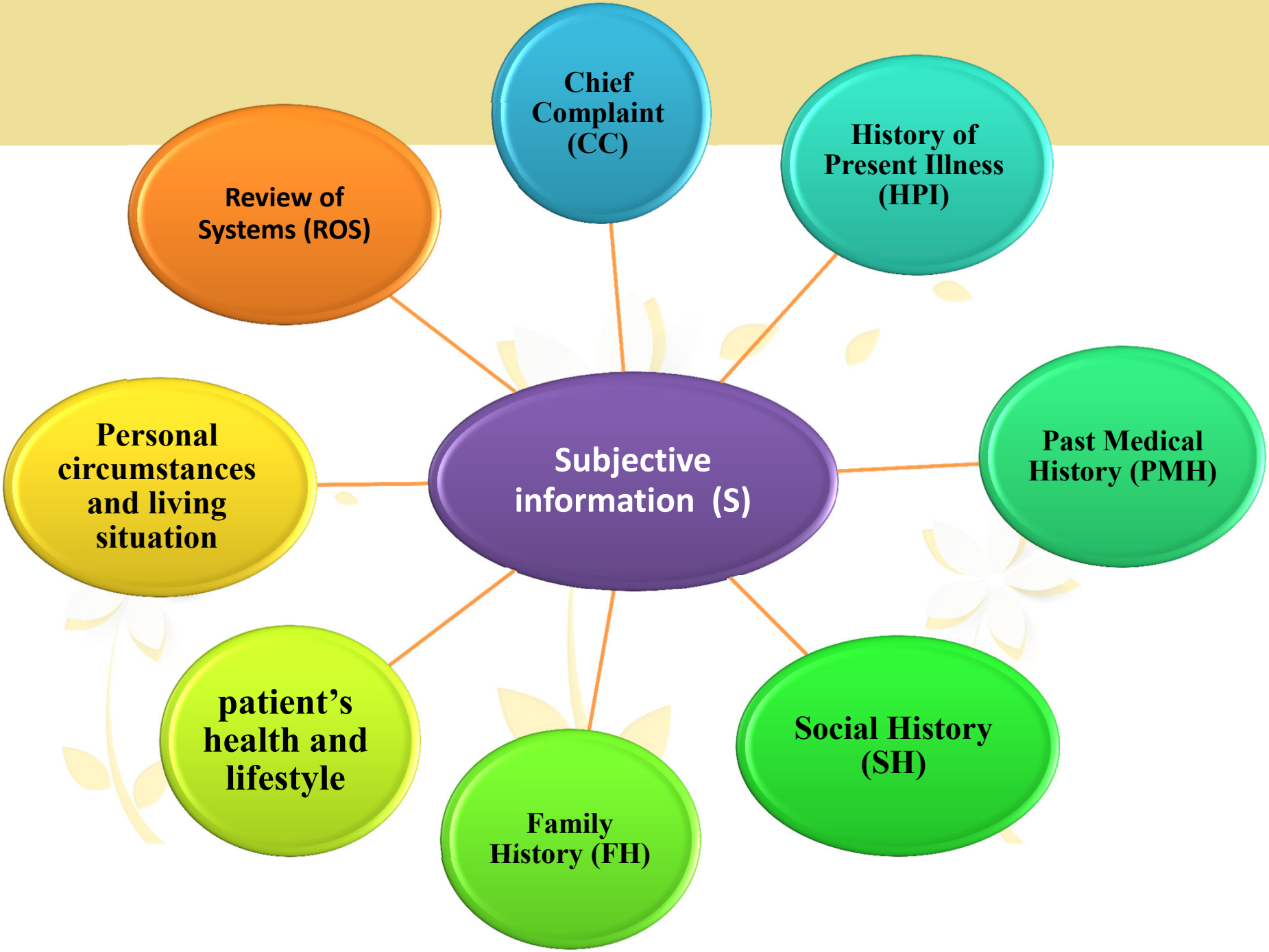
- **Subjective data and Objective data in support of each problem are delineated, an Assessment is made, and a Plan of action identified.**

- **The first letter of the four key words (Subjective, Objective, Assessment, and Plan) serves as the basis for the SOAP acronym.**

Subjective information (S)

- Defined as the information that is provided by the patient and obtained in an interview.

- These are considered non-reproducible data because the information is based on the patient's interpretation and recall of past events.


Chief Complaint (CC)
History of Present Illness (HPI)
Review of Systems (ROS)
Personal circumstances and living situation
Subjective information (S)
Past Medical History (PMH)
patient's health and lifestyle
Family History (FH)
Social History (SH)

Subjective information

- **Chief Complaint (CC):** summary statement of reason for visit, often in patient's own words. E.g., "CC: 'I have a headache'.
- **History of Present Illness (HPI):** Summary of recent history contributing to the CC that is obtained during an interview with the patient and by utilizing open-ended questioning and/or the eight attributes of a symptom. This section is written in a narrative format with full sentences.

Location	Timing/History
Quality	Modifying Factors (Provoking and Palliating)
Severity	Associated Symptoms
Onset/Setting	Meaning to Patient

Subjective information

- **Past Medical History (PMH):** Contains a complete listing of childhood and adult illnesses (both active and resolved), immunization history, and surgical history. If available, each problem should include dates, how long the patient has had it for, and/or if it is resolved. If female, may include information on pregnancies and births. This section is written in a bulleted format.

- **Social History (SH):** Usually written in a narrative format with full sentences, but could also be in bulleted format.

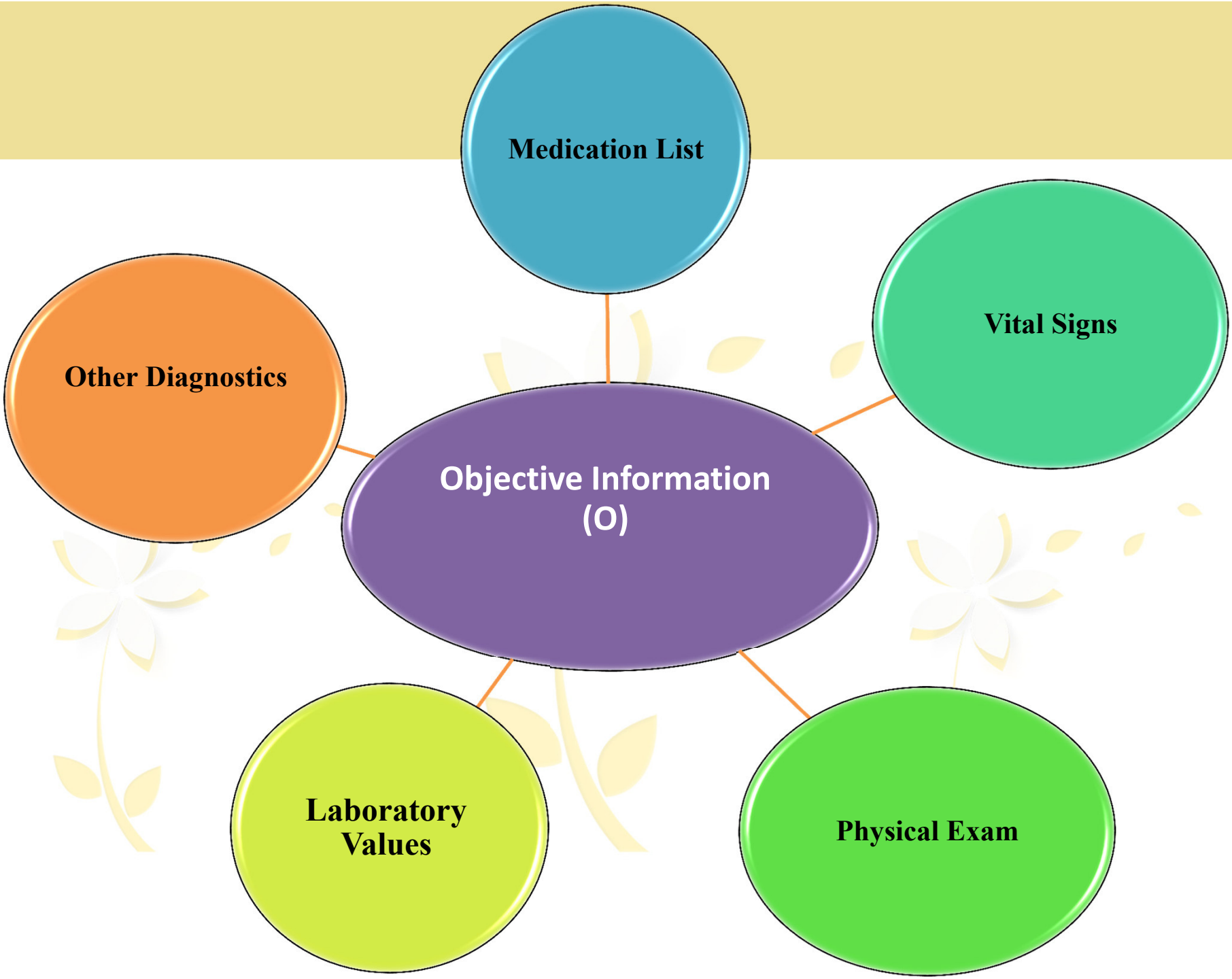
Subjective information

- **Information pertaining to the patient's health and lifestyle:** diet, exercise, substance use (tobacco, alcohol, recreational drugs, and sometimes caffeine).
- **Personal circumstances and living situation:** occupation, residence, mention of family members and/or others who live with the patient and what their role is, sexual orientation and gender identification, and sexual activity.
- **Family History (FH):** Health history of immediate family members, and especially pertinent to any similar problems identified with the patient.

Subjective information

- **Review of Systems (ROS):** Set questions asked that pertain to symptoms associated with each body system. This section is written in a narrative format and will indicate the body system, symptom asked, and which are positive vs. those that the patient denies. The type of questions that should be asked and what is reported will depend on the type of visit.

- E.g. "General: patient denies fevers, weight changes, dizziness, weakness, headaches, and night sweats. Heart: patient denies chest pain, palpitations, SOB, syncope, and swelling."


Medication List
Vital Signs
Other Diagnostics
Objective Information (O)
Laboratory Values
Physical Exam

Objective Information (O)

- Defined as the information obtained by the clinician, any lab work, and diagnostics. Objective data are measurable and reproducible.

- Medication List: Complete list of the current medications the patient is taking. All medications should include the drug name, dose, route, frequency, date started, and (if applicable) the duration of treatment. Compliance to medications and any adverse effects should also be listed here, if obtained. This section is written in a bulleted format.

Objective Information (O)

- **Vital Signs:** BP, HR, RR, Temp, O2. & Wt, Ht, BMI. May also see relevant values from previous visits listed.
- **Physical Exam:** Includes the observations and results of any exams done, formatted as a list.
- **Laboratory Values:** This includes all lab work done recently and is often compared to previous values. Normal and abnormal values will usually be given and is in a list or bulleted format.
- **Other Diagnostics**

Assessment (A)

- This section is where the clinician assimilates all the information they have obtained from the Subjective and Objective areas and applies it to standard practice as defined by evidence-based medicine.

A. **Prioritized problem list and drug related problems:** This list should be complete for all ACTIVE problems for this patient and numerically prioritized according to severity. Generally, the problem associated with the chief complaint will be the highest acuity; however, this is not always the case.

Assessment (A)

- **NOTES for Problem Lists:**
- **Problem titles should be very short and ARE NOT the same thing as symptoms. E.g., "Seasonal Allergies" (NOT itchy eyes, rhinorrhea, sneezing, etc.).**
- **Some problems may be controlled, but if the patient is actively doing something (e.g., taking medication) then it should still be listed. These problems are listed lower in priority, and later on when assessing the problems the documentation can state whether the current regimen is sufficiently controlling the problem.**

Assessment (A)

- **Drug-Related Problems (DRPs):** These problems are associated with and given as sub-bullets to each problem, when applicable. They are short statements that identify areas where drug therapy is contributing to the problem or interfering with desired outcomes. Examples include adverse reactions, drug-drug interactions, drug-disease interactions, sub-optimal therapy, or dosing, etc.

1. Uncontrolled Hypertension: DRP: Combination of ACEi, thiazide, and NSAID can adversely affect renal function
2. Back Pain: DRP: Use of scheduled naproxen can increase BP
3. Pre-Diabetes: DRP: Elevated A1c requires lifestyle modifications and the possible use of metformin”

Assessment (A)

B. Assessment and therapy justification for each problem: Should be numbered and titled according to the problem list in order to connect the assessment with the problem being discussed. The format is generally put into a narrative. The assessment for each problem should include:

i. Initial Assessment: Analysis of the Subjective and Objective information as it pertains to each problem. It is possible that some of the active problems are being appropriately controlled either by lifestyle modifications or by medications. If this is the case, indicating that it's controlled, and how, is all that needs to be communicated.

Assessment (A)

ii. Treatment Goals: This may include short and long-term goals for therapy as it pertains to each problem. Clinical guidelines should be utilized and referenced.

iii. Treatment Options and Justification: Each problem should mention 2-4 different treatment options (pharmacologic and non-pharmacologic) that could be used. This should then be followed up with an explanation for why 1 option is preferable to the others. Examples for justification include clinical guideline recommendations, patient-specific factors, cost, and resolution of DRPs.

Assessment (A) Example

- **Uncontrolled Hypertension:**
- **Initial assessment:** The patient's home BP readings have been ranging from 150-170/96-112 mmHg, with BP of 165/100 mmHg in clinic today. His readings indicate his BP is not at goal per JNC8 guidelines (BP goal of < 140/90 mmHg); despite being at max dose of lisinopril and chlorthalidone, his BP is still elevated. Factors that could be contributing to his elevated BP include the increased use of NSAIDs for back pain and recent diet changes.
- **TTT Goals:** The short-term goal is to control his BP and resolve associated dizziness. Long-term goals are to minimize end organ damage and to prevent cardiovascular mortality.
- **TTT Options:** Naproxen use should be discontinued and back pain and headaches should be evaluated further to find an alternate analgesic. Exercise and dietary changes that reduce sodium should be recommended. If BP continues to be elevated, the addition of a calcium channel blocker (CCB) or a beta blocker (BB) can be added. For this patient, CCBs would be preferred over a BB because of fewer associated side effects and that BBs can reduce exercise tolerance.

Plan (P)

- This section is where the final treatment plan is given for each of the active problems as justified in the assessment. It should also be numbered and titled according to the problem list, and the format is both a list and narrative.
- a. **Treatment Plan:** Contains a list of all the final treatments being chosen. All pharmacologic options should have a complete sig that includes drug name, dose (if weight-based, then dose needs to be calculated), route, frequency, and (when applicable) titrating instructions, the amount, and the duration of treatment. All non- pharmacologic options should include specifics that help to differentiate them from other lifestyle changes.

Plan (P)

- **b. Education and Counseling: Brief mention of the most important key counseling points that should be communicated to the patient for each specific treatment chosen. Information for both pharmacologic and non-pharmacologic therapies should be given.**

Plan (P)

- **C. Monitoring, Follow-Up, and Referrals:** Provides monitoring for both the problem and the treatment plan chosen. Examples include monitoring effectiveness of the plan or needed monitoring for any added medications. Specifics should be given that include what monitoring is being done, time frame for when or if follow-up should happen, and (if applicable) any referrals to other clinicians.
- NOTE: not all problems or plans will need monitoring, follow-up, or referrals. However, if this is the case, it should still be noted in the documentation why monitoring Is not needed.

Plan (P) Uncontrolled Hypertension:

- Discontinue Naproxen
- Encourage a low sodium diet and increased exercise
- Start Amlodipine 5mg PO daily
- Monitoring and Education: Patient should be encouraged to maintain a home BP/HR log. He should be educated on reducing sodium in his diet to less than 2,300 mg a day as recommended by the Dietary Approaches to Stop Hypertension (DASH) diet.
- Additionally, a moderate-intensity exercise regimen of at least 150 minutes/week should be recommended and encouraged. Follow-up can be done by phone in 4-5 days to check resolution of high BP and associated symptoms of dizziness. A CHEM-7 OR SMA-7 should be repeated in 2 weeks in order to reassess renal function and potassium levels.
- CHEM-7 OR SMA-7: Na+, K+, Cl–, bicarbonate (HCO_3^-)- BUN- creatinine & glucose

Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Severity rating of the drug interactions

Rating[a]	Designation	Action	Explanation
Clinically significant drug interaction			
X	Contraindicated	Avoid combination	The drugs are contraindicated for concurrent use.
D	Major	Consider therapy modification	The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse events.
C	Moderate	Monitor therapy	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.
Non-clinically significant drug interaction			
B	Minor	No action needed	The interaction would have limited clinical effects. May include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.
A	Unknown	No known interaction	Unknown.

Notes: [a]A = no known interaction; B = minor/no action needed; C = moderate/monitor therapy; D = major/therapy modification; X = contraindicated/avoid combination.[27]

HYPERTENSION (HTN)

Detection, Evaluation, Pharmacological and Non-pharmacologic Intervention

Dr. Mahmoud Samy, PhD.
Lecturer of Clinical Pharmacy

Outlines

- Definition
- Etiology
- Patient classification and management
- Diagnosis
- Patient Evaluation Objectives
- Pharmacological and Non-pharmacologic Intervention
- Resistant HTN
- HTN Crisis (Urgency & Emergency)

Definition

- **HTN is a persistent, nonphysiologic elevation of BP; it is defined as:**
- **(1) having an systolic blood pressure (SBP) of > 139 (140 mm Hg or greater) (2) having a diastolic blood pressure (DBP) of > 89 (90 mm Hg or greater); or both**
- **(3) taking antihypertensive medication**
- **(4) having been told at least twice by a physician or other health professional that one has HTN.**

Pathophysiology of blood pressure regulation

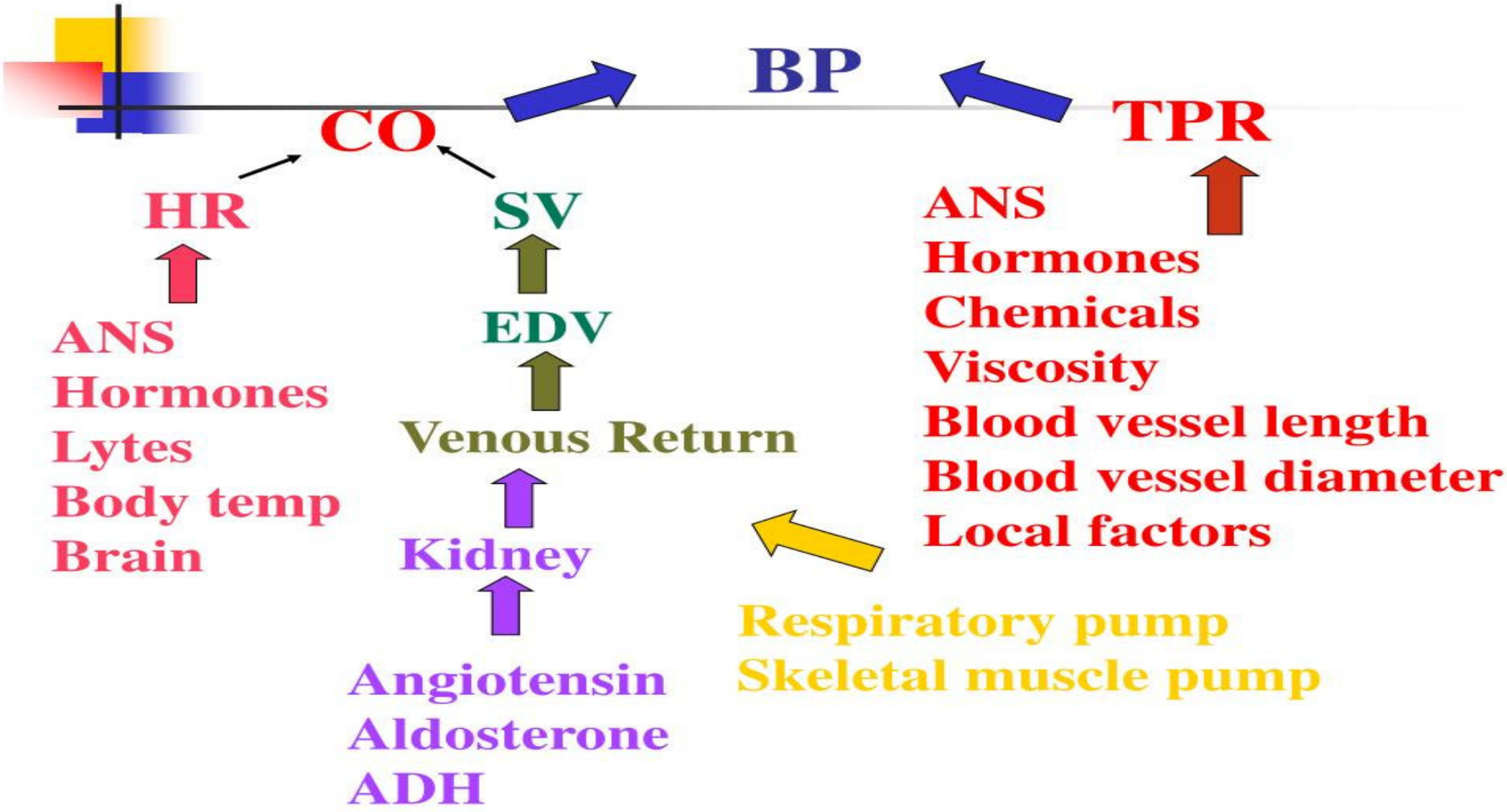
- **Cardiac output and peripheral resistance are the two determinants of arterial pressure.**
- **Cardiac output is determined by stroke volume and heart rate**
- **Stroke volume is related to myocardial contractility and to the size of the vascular compartment.**
- **Peripheral resistance is determined by functional and anatomic changes in small arteries and arterioles.**
- **Various neural and humoral factors are known to influence and regulate BP.**
- **These include the adrenergic nervous system (controls α- and β-adrenergic receptors), the renin–angiotensin–aldosterone system (RAAS) (regulates systemic and renal blood flow), renal function and renal blood flow (influences fluid and electrolyte balance), several hormonal factors (adrenal cortical hormones, vasopressin, thyroid hormone, and insulin), and the vascular endothelium (regulates release of nitric oxide [NO], bradykinin, prostacyclin, and endothelin).**

Pathophysiology of blood pressure regulation

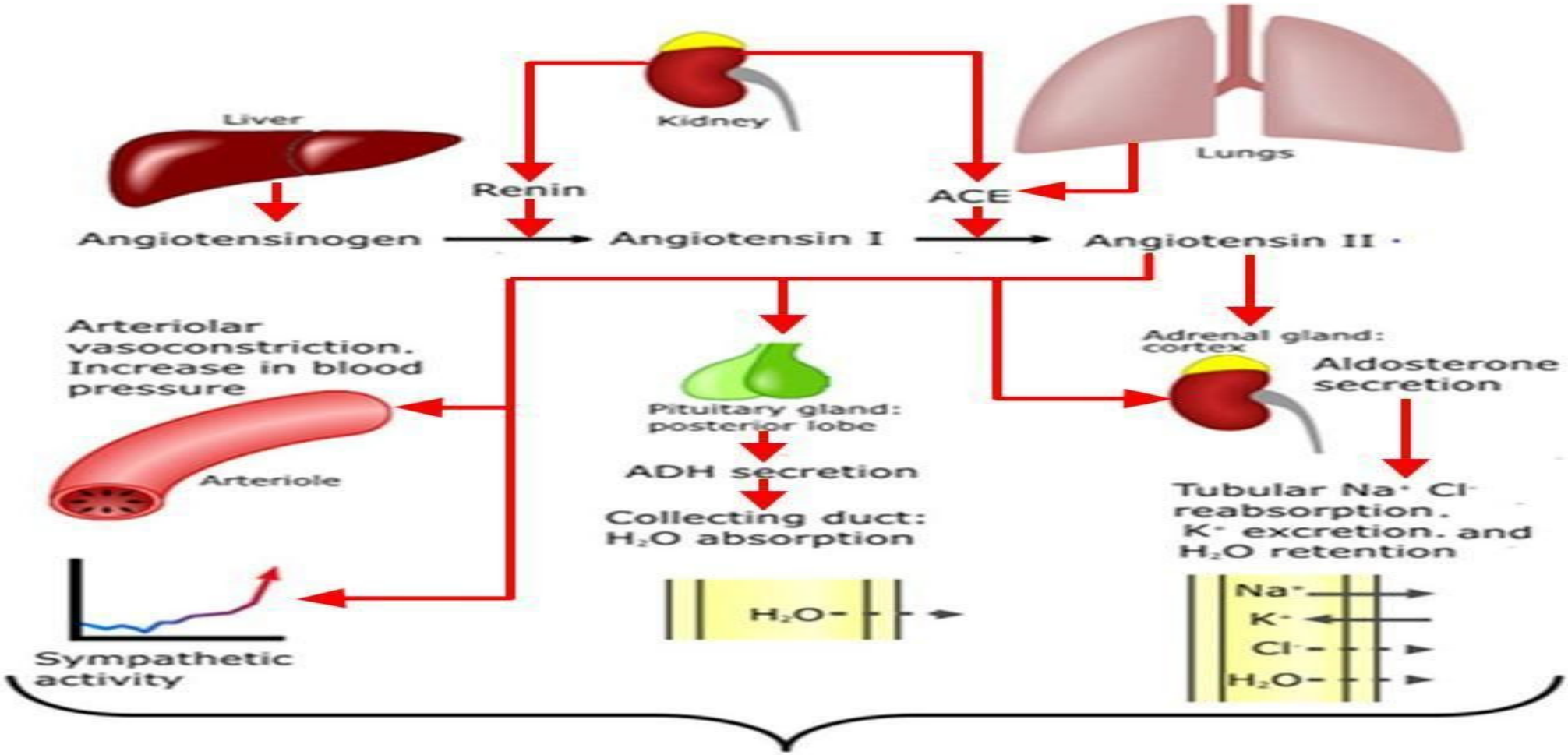
- **Knowledge of these mechanisms is important in understanding antihypertensive drug therapy.**
- **BP is normally regulated by compensatory mechanisms that respond to changes in cardiac demand.**
- **An increase in cardiac output (CO) normally results in a compensatory decrease in total peripheral resistance (TPR); likewise, an increase in TPR results in a decrease in CO. These events regulate MAP, as is represented in the following equation:**

$$MAP = CO \times TPR$$

- **The kidney plays an important role in the regulation of arterial pressure, especially through the RAAS.**



Renin-Angiotensin-Aldosterone System (RAAS)



Water and Sodium retention.
Increased circulating volume. Increased renal perfusion.

Prevalence

- Affects 46% of the population
- Prevalence increases with age
- Major modifiable risk factor for CV disease and stroke

Etiology

- **Essential HTN: 90 – 95 % (no identifiable cause)**

✓**Obesity is a contributor**

✓**Evaluate Na intake**

- **Secondary HTN**

✓**Primary aldosteronism (24 hr aldosterone level)**

✓**Renal parenchymal disease (GFR)**

✓**Renal artery stenosis (GFR)**

✓**Obstructive sleep apnea (Sleep study with oxygen saturation)**

✓**Cushing syndrome (history, dexamethasone suppression test)**

✓**Thyroid or parathyroid disease (TSH, PTH)**

✓**Medications (e.g., cyclosporine, NSAIDs, sympathomimetics) (History, drug screening)**

✓**Pheochromocytoma. (24 hr metanephrine and normetanephrine)**

Patient classification and management

The 2017 11/ American Heart Association (AHA) HTN guideline

BP Classification	SBP (mm Hg)	DBP (mm Hg)	
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Stage 1 hypertension	130-139	Or	80-89
Stage 2 hypertension	≥140	Or	≥ 90
Hypertensive urgency/ emergency	≥ 180	Or	≥ 120

JNC-8, The Eighth Report of the Joint National Committee HTN guideline

BP Classification	SBP (mm Hg)	DBP (mm Hg)	
Normal	< 120	and	< 80
Prehypertension	120-129	Or	80-89
Stage 1 hypertension	140-159	Or	90-99
Stage 2 hypertension	≥160	Or	≥ 100
Hypertensive urgency/ emergency	≥ 180	Or	≥120

European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

ESC/ESH vs. ACC/AHA Hypertension Guideline							
ESC/ESH 2018 (June)				ACC/AHA 2017 (Nov)			
Category	Systolic (mmHg)		Diastolic (mmHg)	Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80	Normal	<120	and	<80
Normal	120-129	and	80-84	Elevated BP	120-129	and	<80
High Normal	130-139	and/or	85-89	Stage 1	130-139	or	80-89
Grade 1	140-159	and/or	90-99	Stage 2	≥140	or	≥90
Grade 2	160-179	and/or	100-109	Hypertensive crisis	≥180	or	≥120
Grade 3	≥ 180	and/or	≥ 110				
Compiled by plexusmd							

BP Classification	SBP (mm Hg)	DBP (mm Hg)	
Normal	< 120	and	< 80
Prehypertension	120-129	Or	80-89
Stage 1 hypertension	140-159	Or	90-99
Stage 2 hypertension	≥160	Or	≥ 100
Hypertensive urgency/ emergency	≥ 180	Or	≥ 120

JNC-8, The Eighth Report of the Joint National Committee HTN guideline

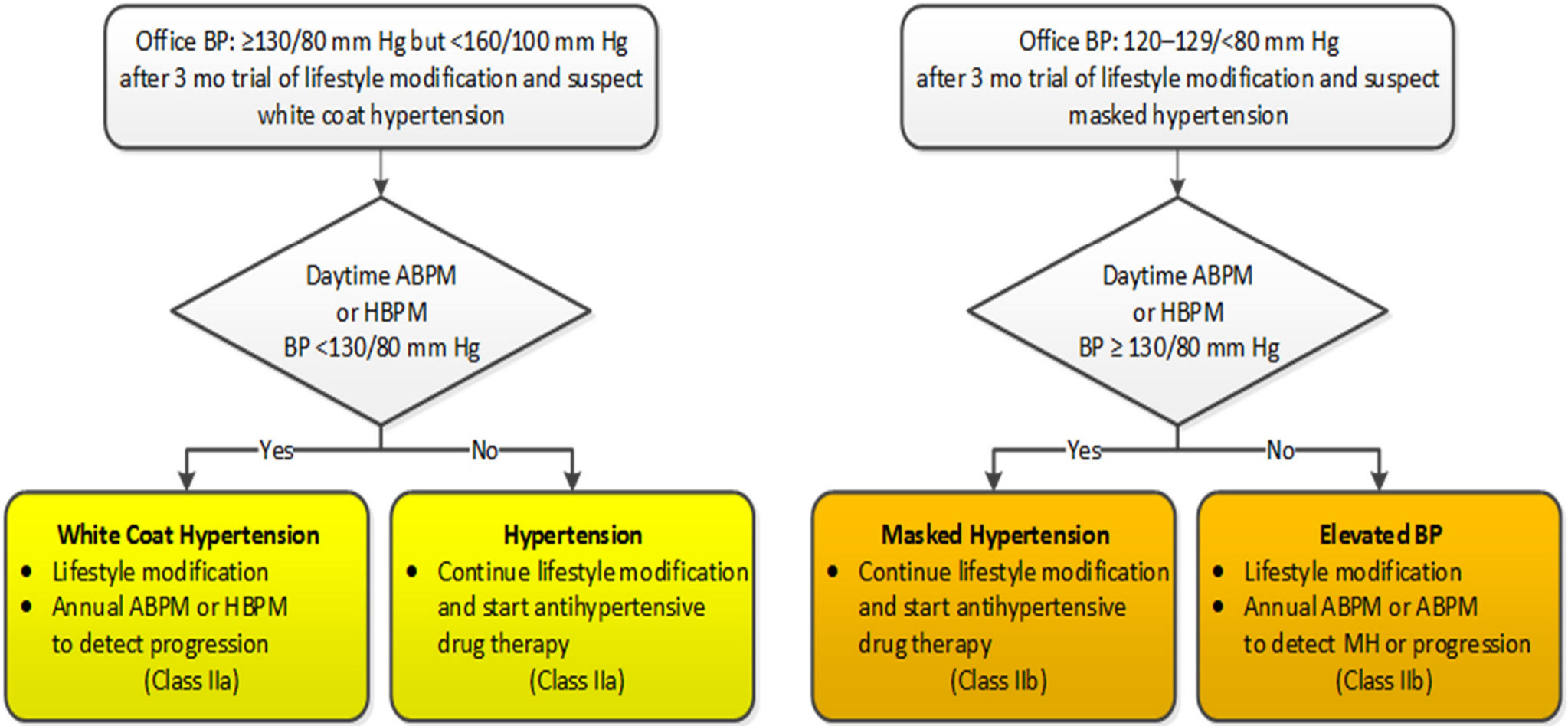
Diagnosis

- Periodic screening for all people older than 21 years
- Patient should be seated quietly in chair for at least 5 minutes.
- Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
- Take BP at least twice, separated by at least 2 minutes.
- The average BP on two separate visits is required to diagnose HTN accurately.
- Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are recommended to confirm diagnosis, screen for white-coat HTN, and screen for masked HTN
- **White-coat HTN**: Office blood pressure is 130/80-160/100 mm Hg after a 3-month trial of life- style modification but with daytime ABPM or HBPM blood pressure less than 130/80 mm Hg AHA / 140/90 mm Hg JNC 8
- **Masked HTN**: Office blood pressure is 120-129/less than 80 mm Hg after a 3-month trial of lifestyle modification; daytime ABPM or HBPM blood pressure of 130/80 AHA 140/90 JNC 8 or greater.

BP Patterns Based on Office and Out-of-Office Measurements

	Office/Clinic/Healthcare Setting	Home/Nonhealthcare/ABPM Setting
Normotensive	No hypertension	No hypertension
Sustained hypertension	Hypertension	Hypertension
Masked hypertension	No hypertension	Hypertension
White coat hypertension	Hypertension	No hypertension

Detection of White Coat Hypertension or Masked Hypertension in Patients Not on Drug Therapy



Pre-HTN & Isolated Systolic Hypertension:

- **Pre-HTN:**

✓**Individuals who are prehypertensive are not candidates for drug therapy but Should be firmly advised to practice lifestyle modification**

✓**Those with pre-HTN, who also have diabetes or kidney disease, drug therapy is indicated if a trial of lifestyle modification fails to reduce their BP to 130/80 mmHg or less.**

- **Isolated Systolic Hypertension:**

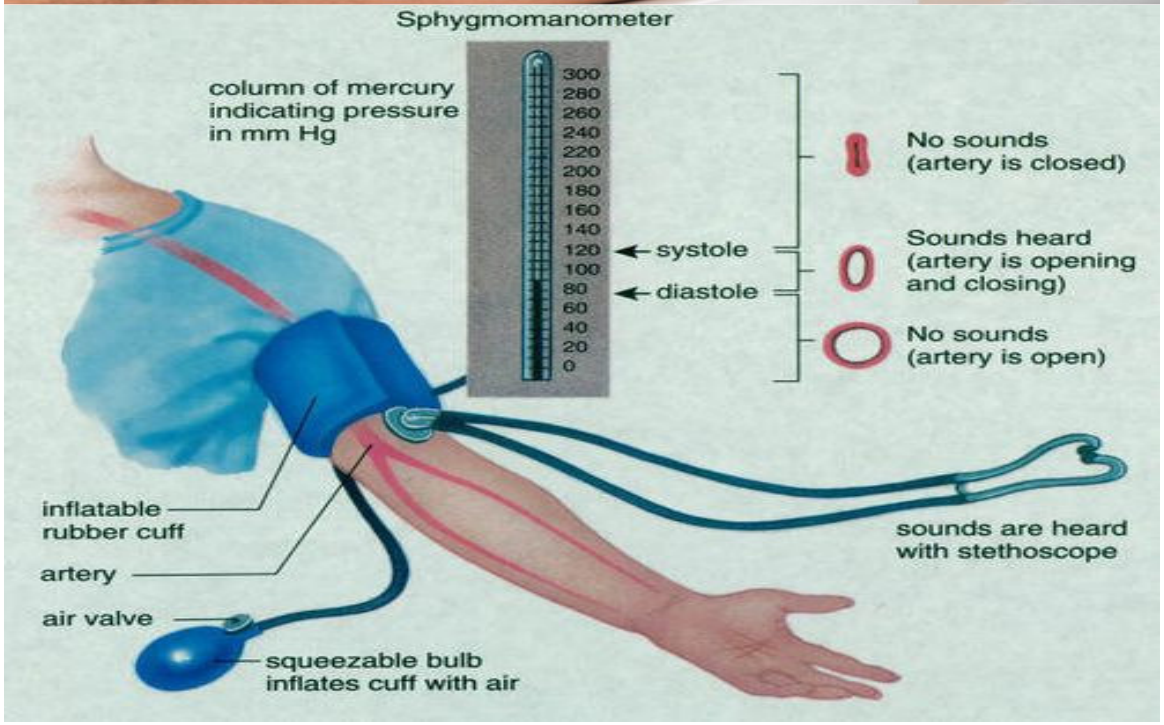
✓**SBP should be primarily considered during treatment and not just diastolic BP.**

✓**Systolic BP is more important after age 50.**

✓**Diastolic BP is more important before age 50.**

Accurate Blood Pressure Measurement

- The equipment should be regularly inspected and validated.
- The operator should be trained and regularly retrained.
- Patient should be seated for 5 minutes with arm bared, unrestricted by clothing, and supported at heart level.
- Smoking or food ingestion should not have occurred within 30 minutes before the measurement
- Bladder evacuation
- The auscultatory method should be used.
- An appropriately sized cuff should be used.
- At least two measurements should be made and the average recorded.
- Clinicians should provide to patients their specific BP numbers and the BP goal of their treatment.


Sphygmomanometer
column of mercury indicating pressure in mm Hg
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
systole
diastole
No sounds (artery is closed)
Sounds heard (artery is opening and closing)
No sounds (artery is open)
inflatable rubber cuff
artery
air valve
squeezable bulb inflates cuff with air
sounds are heard with stethoscope


BLOOD PRESSURE MEASUREMENT

Accurate Blood Pressure Measurement

Phases

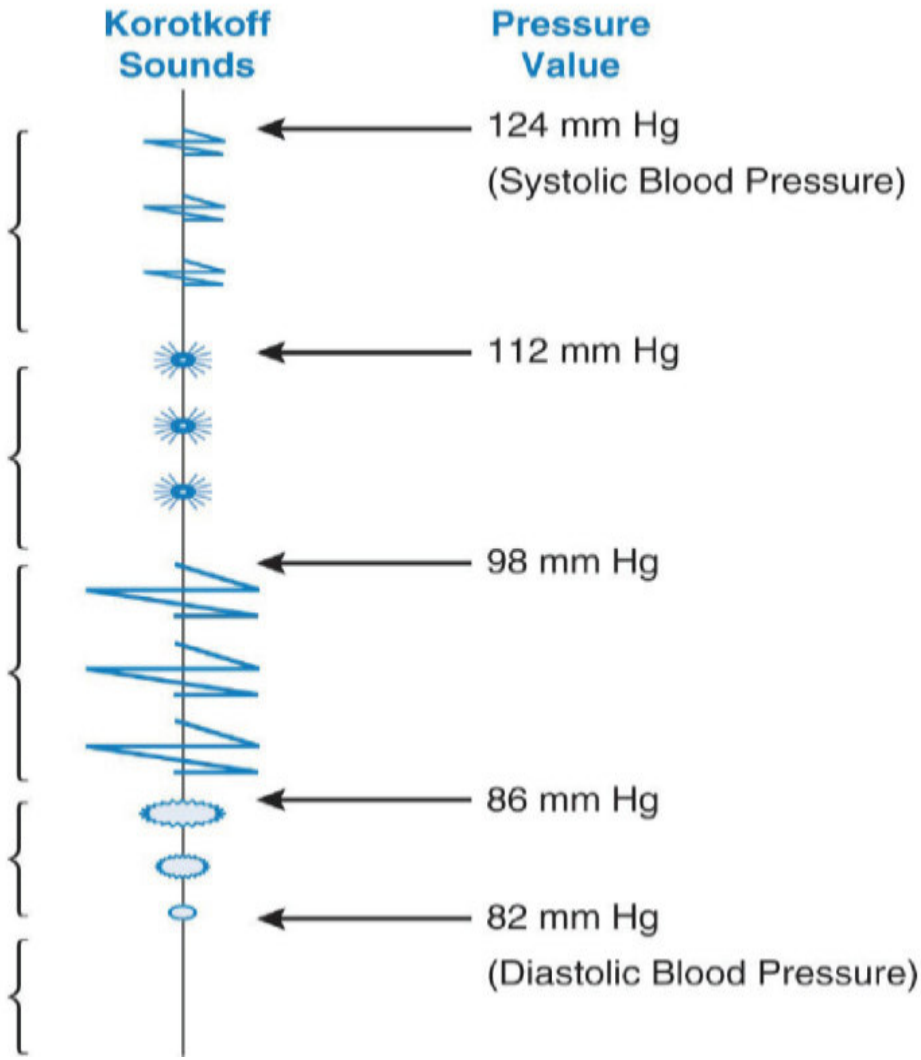
Phase 1: The pressure at which the first faint clear tapping sounds are heard. These sounds gradually increase in intensity as the cuff deflates.

Phase 2: That time during cuff deflation when a murmur or swishing sounds are heard. They are softer and longer than in Phase 1.

Phase 3: The period during which sounds are crisp, loud with increased intensity.

Phase 4: That time when sounds are less distinct, and change to a muffled and soft (or blowing) quality.

Phase 5: The pressure when the last sound is heard and after which all sounds disappear.



BP Measurement Definitions

BP Measurement	Definition
SBP	First Korotkoff sound
DBP	Fifth Korotkoff sound
Pulse pressure	SBP minus DBP
Mean arterial pressure	MAP = (SBP + 2 (DBP))/3 DBP plus one third pulse pressure†
Mid-BP	Sum of SBP and DBP, divided by 2

Patient Evaluation Objectives

- ❑ To assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment
- ❑ To reveal identifiable causes of high BP
- ❑ To assess the presence or absence of target organ damage and CVD

❖**Cardiovascular Risk factors**

✓sex, age, race (non modifiable), total cholesterol, HDL-cholesterol, systolic blood pressure, diabetes, smoking, hypertensive (modifiable).

❖**Target Organ Damage**

✓Heart : Left ventricular hypertrophy, Angina or prior myocardial infarction, Prior coronary revascularization & Heart failure

✓Brain: Stroke or transient ischemic attack

✓Chronic kidney disease

✓Peripheral arterial disease

✓Retinopathy

CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
• Current cigarette smoking, secondhand smoking • Diabetes mellitus • Dyslipidemia/hypercholesterolemia • Overweight/obesity • Physical inactivity/low fitness • Unhealthy diet	• CKD • Family history • Increased age • Low socioeconomic/educational status • Male sex • Psychosocial stress • Race

History

- **Angina/MI Stroke: Complications of HTN, Angina may improve with b-blokers**
- **Asthma, COPD: Preclude the use of b-blockers**
- **Heart failure: ACE inhibitors indication**
- **DM: ACE preferred**
- **Polyuria and nocturia: Suggest renal impairment**
- **Claudication: May be aggravated by b-blockers**
- **Gout: May be aggravated by diuretics**
- **Use of NSAIDs: May cause or aggravate HTN**
- **Family history of HTN: Important risk factor**
- **Family history of premature death: May have been due to HTN**
- **Family history of DM : Patient may also be Diabetic**
- **Cigarette smoker: Aggravate HTN, independently a risk factor for CAD and stroke**
- **High alcohol: A cause of HTN**
- **High salt intake: Advice low salt intake**

Examination

- Appropriate measurement of BP in both arms
- Optic fundi
- Calculation of BMI (waist circumference also may be useful)
- Auscultation for carotid, abdominal, and femoral bruits
- Palpation of the thyroid gland.
- Thorough examination of the heart and lungs
- Abdomen for enlarged kidneys, masses, and abnormal aortic pulsation
- Lower extremities for edema and pulses
- Neurological assessment

Basic and Optional Laboratory Tests for Primary Hypertension

Basic testing	**Fasting blood glucose***
	Complete blood count
	Lipid profile
	Serum creatinine with eGFR*
	Serum sodium, potassium, calcium*
	Thyroid-stimulating hormone
	Urinalysis
	Electrocardiogram
Optional testing	**Echocardiogram**
	Uric acid
	Urinary albumin to creatinine ratio

Benefits of treating elevated BP

- Decreased risk of stroke
- Decreased risk of myocardial infarction (MI)
- Decreased risk of heart failure (HF)

Effects of lifestyle modifications on BP

Modification	Recommendation	Approximate SBP Reduction
Weight reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m2)	**5–20 mm Hg per 10-kg weight loss**
Adopt Dietary Approaches to Stop Hypertension (DASH) eating plan (includes substantial K intake)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	**8–14 mm Hg**
Reduce Na intake	Reduce Na intake to < 1500 mg/day Reducing Na intake by at least 1000 mg/day will lower BP	**2–8 mm Hg**
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)	**4–9 mm Hg**
Moderation of alcohol consumption	**Limit consumption to:** **Men: 2 drinks/day (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey)** **Women and those of lower body weight: 1 drink/day**	**2–4 mm Hg**

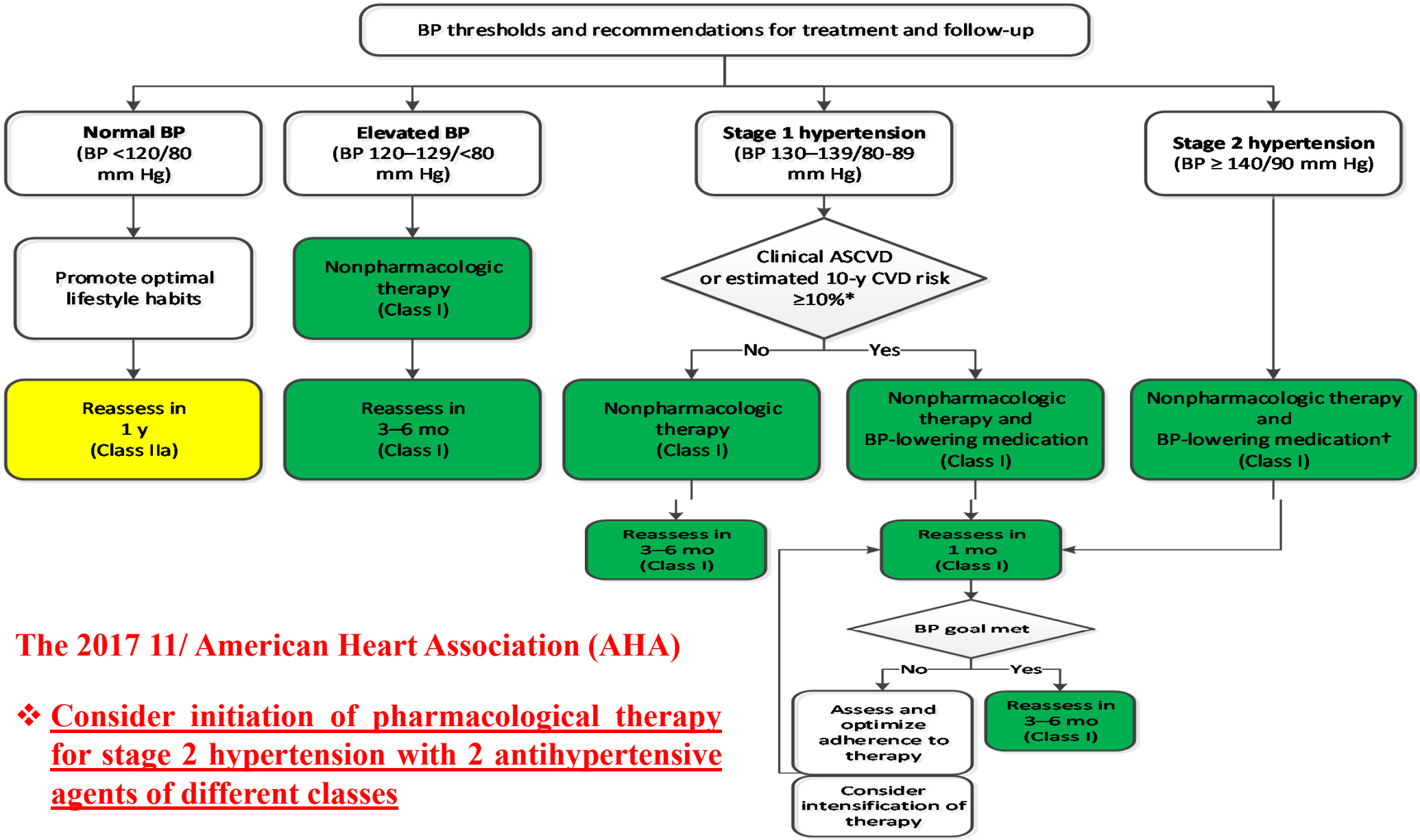
BP Thresholds for Goals of Pharmacologic Therapy in Patients with HTN According to Clinical Condition

The 2017 11/ American Heart Association (AHA) HTN guideline

Clinical Condition	BP Threshold, mm Hg	BP Goal, mm Hg
Clinical cardiovascular disease (CVD) or 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥10%	≥130/80	<130/80 for all
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	
Diabetes mellitus	≥130/80	
Chronic kidney disease	≥130/80	
Chronic kidney disease after renal transplantation	≥130/80	
Heart failure	≥130/80	
Stable ischemic heart disease	≥130/80	
Secondary stroke prevention	≥140/90	
Secondary stroke prevention (lacunar)	≥130/80	
Peripheral arterial disease	≥130/80	
Older persons (≥65 years; noninstitutionalized, ambulatory, community-living)	≥130 (SBP)	<130 (SBP)

JNC-8, The Eighth Report of the Joint National Committee HTN guideline

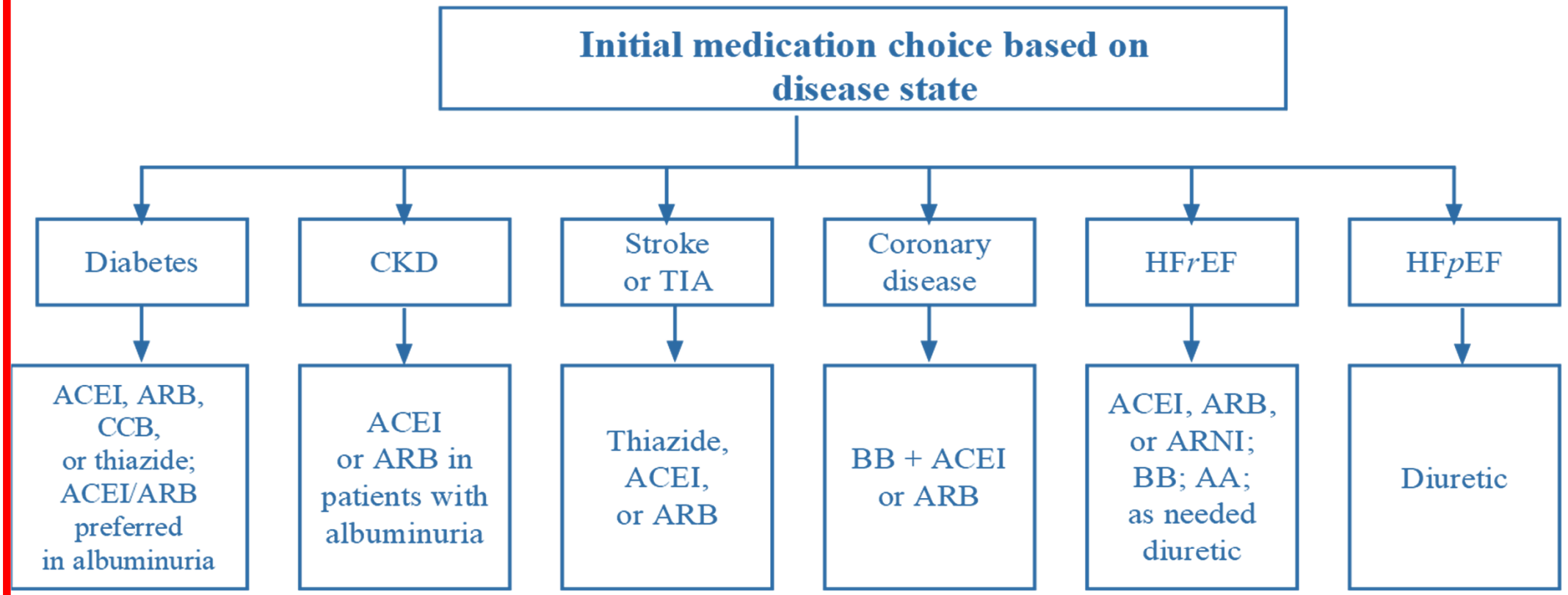
- < 150/90 mm Hg for patients ≥ 60
- < 140/90 mm Hg for patients < 60, diabetes, and chronic kidney disease



The 2017 11/ American Heart Association (AHA)

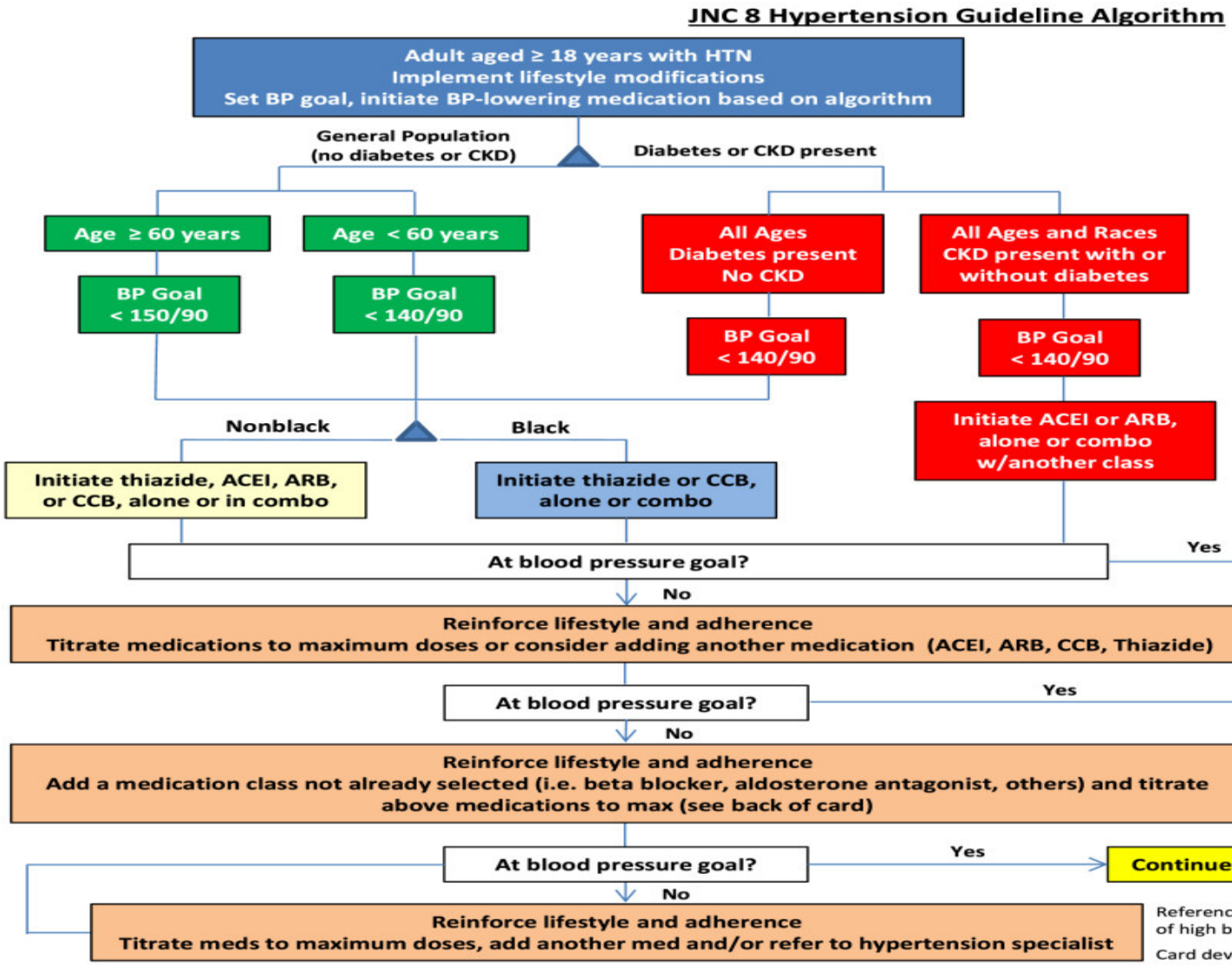
- **Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes**

First-line agents for patients with comorbidities is described as follow:



AA = aldosterone antagonist; ACEI = angiotensin-receptor converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = β-blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; HF*p*EF = heart failure with preserved ejection fraction; HF*r*EF = heart failure with reduced ejection fraction; TIA = transient ischemic attack.

JNC 8



Initial Drugs of Choice for Hypertension
- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Thiazide diuretic
- Calcium channel blocker (CCB)

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug.
B	Start one drug, then add a second drug before achieving max dose of first
C	Begin 2 drugs at same time, as separate pills or combination pill. **Initial combination therapy is recommended if BP is greater than 20/10mm Hg above goal**

Lifestyle changes:
- Smoking Cessation
- Control blood glucose and lipids
- Diet
  - ✓Eat healthy (i.e., DASH diet)
  - ✓Moderate alcohol consumption
  - ✓Reduce sodium intake to no more than 2,400 mg/day
- Physical activity
  - ✓Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session.

Reference: James PA, Ortiz E, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014 Feb 5;311(5):507-20

Card developed by Cole Glenn, Pharm.D. & James L Taylor, Pharm.D.

First line agents

- **Thiazides & thiazide like diuretics (Chlorthalidone, Hydrochlorothiazide, Indapamide)**

✓**Mechanism of action: Inhibit reabsorption of Na in in the distal tubule. They induce a natriuresis that causes diuresis and decreases plasma volume and CO.**

✓**Can worsen gout by increasing serum uric acid**

✓**Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy**

✓**Greater risk of developing DM; use caution in patients at high risk of DM (e.g., family history, obesity)**

✓**S.E: Hypokalemia, hyponatremia, hyperglycemia, hypovolemia, pancreatitis, photosensitivity, hypercholesterolemia, hypertriglyceridemia, hyperuricemia with gout, orthostatic hypotension (more frequent in elderly)**

✓**Can assist in the management of osteoporosis by preventing urine calcium loss**

Diuretics and Recommended Dosing

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)				
Hydrochlorothiazide	65–75	25 mg daily or BID	100	6–12
Indapamide	93	1.25 Daily	5	8 - 12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide	30–50	250–500 daily or BID	2000	6–12

ACE inhibitors

- The ACEIs directly inhibit ACE, blocking the conversion of angiotensin I to angiotensin II. This action reduces angiotensin II-mediated vasoconstriction and aldosterone secretion and ultimately lowers BP.
- Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.
- Inhibiting ACE also prevents the breakdown and inactivation of bradykinin, which may lead to additive vasodilation by enhancing NO & Prostaglandins. However, bradykinin accumulation can also cause a nonproductive cough in some patients.
- Noscapine, possibly by inhibition of bradykinin synthesis, eliminates ACEI-induced cough in the majority of patients and allows them to continue with ACEI therapy
- C.I: Avoid initiation with systolic BP <100 mm Hg, pregnancy, acute renal failure, angioedema, bilateral renal stenosis, serum potassium ≥ 5.5 mEq/L.
- Aspirin and NSAIDs (DDI)

ACE inhibitors

Drug	Starting Dosage	Target Dosage	Maximal Dosage
Captopril	6.25- 12.5 mg three times daily	50 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 mg twice daily	20 mg twice daily
Lisinopril	2.5–5 mg daily	20 mg daily	40 mg daily
Perindopril	2 mg daily	8 mg daily	16 mg daily
Ramipril	1.25–2.5 mg daily	10 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily	4 mg daily

Angiotensin receptor blockers (ARBs)

- The ARBs modulate the RAAS by directly blocking the angiotensin II type 1 receptor site, preventing angiotensin II-mediated vasoconstriction and aldosterone release. Overall, ARBs are the best tolerated of the first-line agents. They do not affect bradykinin.
- Avoid in pregnancy, bilateral renal stenosis, serum potassium ≥ 5.5 mEq/L.

Drug	Starting Dosage	Target Dosage
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	20–40 mg twice daily	160 mg twice daily
Telmisartan	40 mg Daily	20–80 mg Daily
Olmesartan medoxomil	20 mg Daily	20–40 Daily
Irbesartan	150 Daily	75–300 mg Daily

Direct renin antagonist (Aliskiren)

- **Aliskiren is the only direct renin inhibitor. Similar to an ACEI or ARB, this agent is a Renin-angiotensin-aldosterone system (RAAS) inhibitors (RAAS) blocker. It is approved for treatment of hypertension and has been studied in combination with an ACEI, ARB, or thiazide diuretic.**
- **Contraindicated in pregnancy**
- **Contraindicated in patients with DM when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension**
- **Avoid use in combination with cyclosporine or itraconazole.**
- **Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).**
- **Aliskiren dose 150–300mg Daily**

Calcium channel blockers

- **i. Dihydropyridine CCBs: Amlodipine, felodipine, nifedipine, Nicardipine**

✓**Often used to reduce systemic vascular resistance and arterial pressure.**

✓**Nicardipine is more selective for cerebral and coronary blood vessels.**

✓**Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension**

✓**Useful for isolated systolic hypertension or use in African American patients**

Calcium channel blockers

- **ii. Nondihydropyridine CCBs: Diltiazem, verapamil**

✓**Relatively selective for myocardium, reduce myocardial oxygen demand and reverse coronary vasospasm, and are often used to treat angina.**

✓**Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g., atrial fibrillation, stable angina)**

✓**Diltiazem: By having both cardiac depressant and vasodilator actions, are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.**

✓**Contraindicated in heart block and sick sinus syndrome**

✓**Potential drug interactions due to CYP450 inhibition**

✓**Side effects: constipation (verapamil) , peripheral edema & Gingival overgrowth.**

Second-Line Agents

- **a. β-Blockers**

✓**Atenolol, Acebutolol, Betoxolol, Nadolol, Bisoprolol, Carvedilol, Labetalol Nebivolol, Metoprolol Succinate, Propranolol.**

✓**Labetalol and carvedilol are β-blockers that also have α1- receptor blocking activity.**

✓**β-Blockers have several direct effects on the CV system. They can decrease cardiac contractility and CO, lower heart rate, blunt sympathetic reflex with exercise, reduce central release of adrenergic substances, inhibit norepinephrine release peripherally, and decrease renin release from the kidney.**

✓**Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.**

✓**C.I: Severe asthma, second- or third degree heart block, acute left ventricular dysfunction exacerbation.**

Second-Line Agents

- **a. β-Blockers**

✓ **Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity) (block the release of insulin by interacting with nerve signals to the pancreas)**

✓ **Can mask some signs of hypoglycemia in patients with DM (mainly by keeping the heart rate slow, They may also inhibit the release of glucose from the liver).**

✓ **Can cause depression**

✓ **Other S.E: aggravation of peripheral arterial disease, erectile dysfunction, increased triglycerides, decreased HDL-C**

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily
Carvedilol CR	10 mg daily	80 mg daily
Metoprolol succinate	12.5–25 mg daily	200 mg daily
Atenolol	25 mg Daily to BID	100 mg Daily to BID
Nebivolol	5 mg Daily	10 mg Daily
Propranolol	40 mg Daily (LA and XL) or BID.	180 mg Daily (LA and XL) or BID.

Second-Line Agents

- **b. Aldosterone Antagonists (Spironolactone and eplerenone)**

✓**Potent blockade of the aldosterone receptor inhibits sodium and water retention and inhibits vasoconstriction. These agents are also considered potassium-sparing diuretics.**

✓**Hyperkalemia is a known dose-dependent effect with aldosterone antagonists and is more prominent in patients with CKD or in patients taking a concurrent RAAS blocking agent (ACEI, ARB, or direct renin inhibitor).**

✓**Gynecomastia is a side effect of spironolactone, usually more common with higher doses, that does not occur with eplerenone.**

✓**Other S.E: Hyperkalemia, hyponatremia.**

	eGFR ≥ 50 mL/min/1.73 m^2		eGFR 30-49 mL/min/1.73 m^2	
	Initial dose	Maintenance dose	Initial dose	Maintenance dose
Eplerenone	25 mg daily	50 mg daily	25 mg every other day	25 mg daily
Spironolactone	12.5–25 mg daily	25 mg daily or BID	12.5 mg daily or every other day	12.5–25 mg daily

Other Agents

- **Loop diuretics (e.g., furosemide and torsemide)**

✓**Can be used in some patients for hypertension.**

✓**Mechanism of action: Inhibit reabsorption of Na in the ascending limb of the loop of Henle (loops)**

✓**They should generally be reserved for patients with heart failure or severe CKD in whom their diuretic action remains prolonged.**

✓**Because they are more potent at inducing diuresis compared with thiazide diuretics, they can cause more electrolyte disturbances (e.g., hypokalemia).**

✓**S.E: Hypokalemia, hypocalcemia, hyponatremia, hyperglycemia, hypovolemia, pancreatitis, photosensitivity, hypercholesterolemia, hypertriglyceridemia, hyperuricemia with gout, orthostatic hypotension (more frequent in elderly).**

Other Agents

- Loop diuretics (e.g., furosemide and torsemide)

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide	10–67	20–40 mg daily or BID	600	6–8
Bumetanide	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid	100	25–50 mg daily or BID	200	6–8

Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.

Other Agents

- **α-Blockers (e.g., doxazosin, prazosin, and terazosin)**

✓**Attach to peripheral α1- receptors, inhibiting the uptake of catecholamines in smooth muscle, and cause vasodilation.**

✓**Although effective in lowering BP, they have more side effects than first-line or second-line agents.**

✓**The most prominent side effect is hypotension, which is most evident after the first dose and with postural changes (arising from a lying position to a standing position).**

✓**Doxazosin 1–8 Daily, Prazosin 2–20 BID to TID & Terazosin 1–20 Daily to BID**

Other Agents

- **CENTRAL α2-AGONISTS (e.g., Clonidine, and Methyldopa)**

✓**Stimulation of α2-receptors in the CNS inhibits sympathetic outflow (via negative feedback) to the heart, kidneys, and peripheral vasculature, resulting in peripheral vasodilation.**

✓**Clonidine should be started at a low dosage and gradually increased to achieve optimal BP lowering with minimal side effects. The immediate-release tablet is started as 0.1 mg twice daily, with 0.1- or 0.2-mg/day increases every 2 to 4 weeks until his BP goal is achieved or side effects appear.**

✓**Methyldopa has been extensively evaluated and is considered safe in pregnancy. Therefore, it is recommended as a first-line agent when hypertension is first diagnosed during pregnancy. The usual initial dose is 250 mg administered twice daily up to 2,000 mg/day.**

✓**Methyldopa causes side effects similar to those associated with clonidine, including sedation, lethargy, postural hypotension, dizziness, dry mouth, headache, and rebound hypertension**

Other Agents

- **ARTERIAL VASODILATORS (e.g., Hydralazine and Minoxidil)**

✓**Hydralazine causes direct relaxation of arteriolar smooth muscle. Arterial vasodilators are infrequently used, except for patients with severe CKD.**

✓**This vasodilation, however, stimulates the sympathetic nervous system and results in a reflex tachycardia.**

✓**Hydralazine on of the drugs-induced lupus**

✓**Minoxidil, a potent arterial vasodilator, is similar to hydralazine**

✓**Hypertrichosis is a common adverse effect of oral minoxidil, occurring in 80% to 100% of patients.**

✓**Topical minoxidil is an approved therapy for male pattern baldness, but topical administration does not provide BP-lowering effects.**

✓**Fluid retention with minoxidil is common, presenting as edema and weight gain.**

Considerations within specific patient populations

- **Patients with coronary heart disease (CHD):** Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)

- **Older adult patients:** Caution with antihypertensive agents and orthostatic hypotension.

Considerations within specific patient populations

- **Black patients:**

✓β-Blockers and ACE inhibitors are generally less effective as monotherapy than in non–black patients.

✓In black adults with HTN but without HF or CKD, including those with diabetes mellitus, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. β-blockers and ACE inhibitors should still be used if comorbid conditions dictate.

- **Women**

✓Oral estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.

✓HTN increases the risk to mother and fetus in women who are pregnant. Preferred medications include **methyldopa, nifedinpine and labetalol**.

✓Methyldopa 250–1,000 BID

✓ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects.

Monitoring

- **Have the patient return in 4 weeks to assess efficacy (sooner if clinically indicated).**
- **If there is an inadequate response with the first agent with optimal dosing (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class while continuing initial therapy.**

Patient Education

- Assess patient's understanding and acceptance of the diagnosis of hypertension
- Assure patient understands his or her goal BP value
- Inform patient about recommended treatment, including lifestyle modification.
- Provide specific written information using standard brochures when available
- Emphasize the need to continue treatment
- Emphasize that control does not mean cure
- Emphasize that elevated BP is usually not accompanied by symptoms
- Encourage self-monitoring with validated BP devices
- Minimize the cost of therapy, when possible
- Discuss adherence at each clinical encounter
- Encourage gradual sustained weight loss
- Simplify the regimen to once-daily dosing, whenever possible
- Incorporate treatment into patient's daily lifestyle

Resistant HTN

- **a. Confirm diagnosis**

✓**AHA guidelines: Office BP of 130/80 mm Hg or greater and patient taking at least three antihypertensive medications at optimal doses, including a diuretic (confirmed adherence) OR Office BP of <130/80 mm Hg but patient requires at least four antihypertensive medications**

✓**JNC-8 Hypertension: Office BP of 140/90 mm Hg or greater and patient taking at least three antihypertensive medications at optimal doses, including a diuretic (confirmed adherence) OR Office BP of <140/90 mm Hg but patient requires at least four antihypertensive medications**

- **b. Exclude pseudoresistance**

✓**Ensure accurate office BP readings**

✓**Exclude white-coat HTN**

✓**Ensure adherence**

Resistant HTN

- **c. Identify and reverse contributing factors**

❖**i. Lifestyle factors**

✓**Obesity**

✓**High-salt, low-fiber diet**

✓**Physical inactivity**

✓**Excessive alcohol use**

❖**ii. Interfering medications**

✓**NSAIDs**

✓**Sympathomimetics**

✓**Stimulants**

✓**Oral contraceptives**

Resistant HTN

- d. Screen and treat for secondary causes of HTN
- e. Assess for target organ damage
- f. Pharmacological treatment
- i. Maximize diuretic therapy

✓ (a) Use thiazide or thiazide-like diuretics if eGFR > 30 mL/min/m2

✓ (1) Chlorthalidone and indapamide have the most evidence for reducing cardiovascular outcomes

✓ (2) Chlorthalidone is more effective at inducing predictable natriuresis in patients with an eGFR 30-45 mL/min/m2

✓ (b) Use loop diuretics if eGFR < 30 mL/min/m2

✓ ii. Add mineralocorticoid receptor antagonists (MRA) (spironolactone or eplerenone)

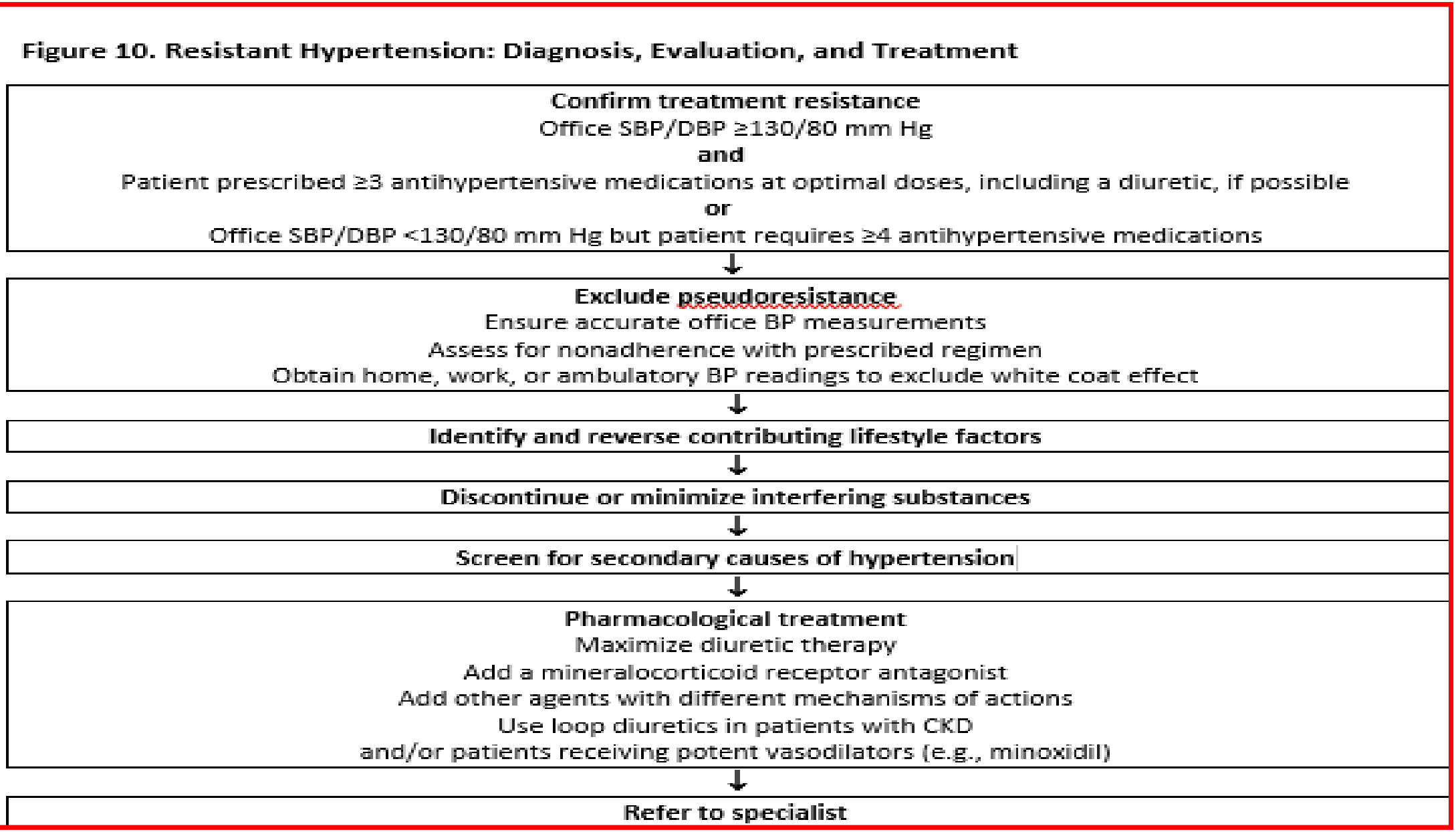
✓ iii. Alter dosing times to include a nocturnal dose or divide doses of drugs with half-lives <12-15 hours

✓ iv. Add other agents from different drug classes

✓ v. Addition of hydralazine or minoxidil requires concomitant use of a ß-blocker and diuretic

- g. Follow-up
- i. Ensure attainment of target BP after six months of therapy

Figure 10. Resistant Hypertension: Diagnosis, Evaluation, and Treatment



HYPERTENSIVE CRISES

- **Hypertensive urgency**

✓**Hypertensive urgency is defined as a diastolic blood pressure of 110 mm Hg or greater without the acute target-organ damage or dysfunction**

✓**Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.**

✓**Treated by reinstitution or intensification of antihypertensive drug therapy**

✓**No indication for referral to the ED, immediate reduction in blood pressure in the ED, or hospitalization**

✓**No proven benefit exists from rapid reductions in blood pressure.**

✓**Choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate.**

✓**All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).**

HYPERTENSIVE CRISES

- **Hypertensive emergency**

✓**Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage**

✓**Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, or other acute neurologic deficit; acute MI; acute left ventricular (LV) failure with pulmonary edema; dissecting aortic aneurysm; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia**

✓**Actual blood pressure may not be as important as the rate of blood pressure rise.**

✓**Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage**

✓**In general, oral therapy is discouraged for hypertensive emergencies.**

HYPERTENSIVE CRISES

- **Hypertensive emergency**

✓**Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.**

✓**Patients are usually admitted for intensive care unit care and close follow-up.**

✓**Lower mean arterial pressure (MAP) by no more than 25% in the first hour; then reduce SBP to 160 mm Hg and DBP to 100–110 mm Hg over next 2–6 hours; then to normal over next 24–48 hours.**

$$MAP = (SBP + 2\,(DBP))/3$$

✓**MAP, or mean arterial pressure, is defined as the average pressure in a patient's arteries during one cardiac cycle. It is considered a better indicator of perfusion to vital organs than systolic blood pressure (SBP).**

HYPERTENSIVE CRISES

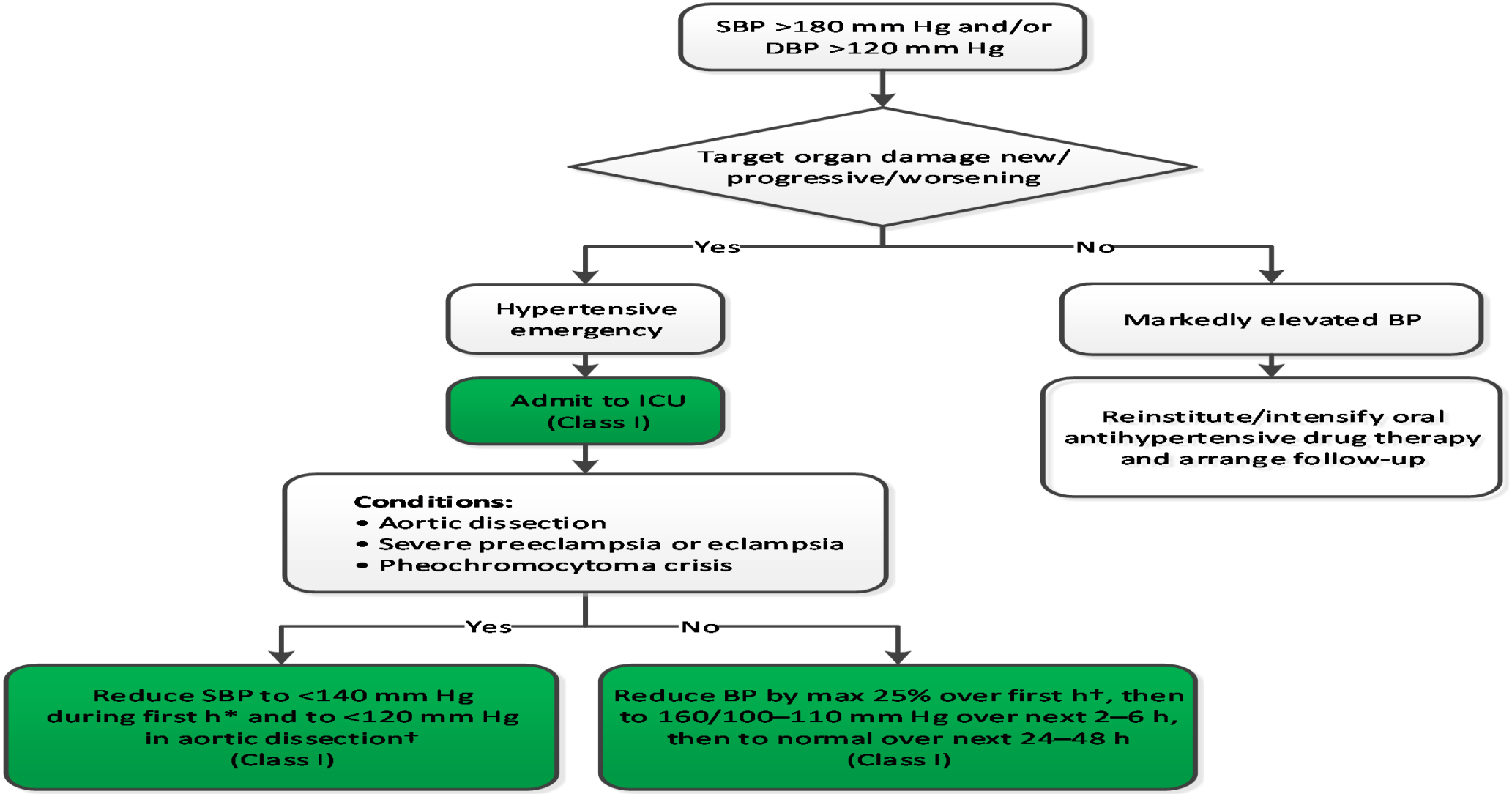
- **Hypertensive emergency**
- **Exceptions:**

✓**Do not lower blood pressure in acute ischemic stroke unless greater than 220/120 mm Hg or greater than 185/110 mm Hg in tissue plasminogen activator candidates.**

✓**Rapidly lower blood pressure to less than 140 mm Hg in the first hour of treatment in severe preeclampsia or eclampsia and in pheochromocytoma with hypertensive crisis.**

✓**Rapidly lower blood pressure to less than 120 mm Hg in the first hour of treatment in aortic dissection.**

Diagnosis and Management of a Hypertensive Crisis



Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Sodium nitroprusside (immediate, 2–3 min)	0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; max 10 mcg/kg/min; for infusion rates ≥ 4–10 mcg/kg/min or duration > 30 min, thiosulfate can be coadministered to prevent cyanide toxicity	Intra-arterial BP monitoring recommended to prevent "overshoot"; lower doses required in older adult patients; tachyphylaxis common with extended use. AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurologic changes and cardiac arrest, nausea, vomiting, methemoglobinemia CIs: Renal, hepatic failure Caution: Elevated ICP
Nitroglycerin (2–5 min, 5–10 min)	5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a max 20 mcg/min	Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients AEs: Headache, nausea, vomiting, tachyphylaxis
Hydralazine (10 min, 1–4 hr)	5–10 mg by slow IV infusion every 4–6 hr (initial 20 mg/dose)	BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent AEs: Reflex tachycardia, headache, flushing Caution: Angina or MI, elevated ICP

Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
ACEI		
Enalaprilat (within 30 min, 12–24 hr)	0.625–1.25 mg over 5 min; doses can be increased up to max 5 mg every 6 hr	Should not be used in acute MI; mainly useful in hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min) and unpredictability of BP response AEs: Renal insufficiency or failure, hyperkalemia CIs: Pregnancy, bilateral renal artery stenosis, angioedema (Note: Long half-life)
Dopamine agonist		
Fenoldopam (< 5 min, 30 min)	0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a max of 1.6 mcg/kg/min	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or ICP and those with sulfite allergy AEs: Headache, flushing, tachycardia, cerebral ischemia

Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
DHP CCBs		
Nicardipine (1–5 min, 15–30 min; up to 4 hr if prolonged infusion)	5 mg/hr, increased by 2.5 mg/hr every 5 min to a max 15 mg/hr	Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients AEs: Reflex tachycardia, nausea, vomiting, headache, flushing Caution: Angina or MI, acute HF
Clevidipine (2–4 min, 5–15 min)	1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; max 32 mg/hr; max duration 72 hr	Patients with renal failure and hepatic failure and older adults not specifically studied – use low-end range for older adults. contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis) Caution: HF, concomitant β-blocker use, reflex tachycardia, rebound HTN

Commonly Used IV Drugs for Hypertensive Emergencies

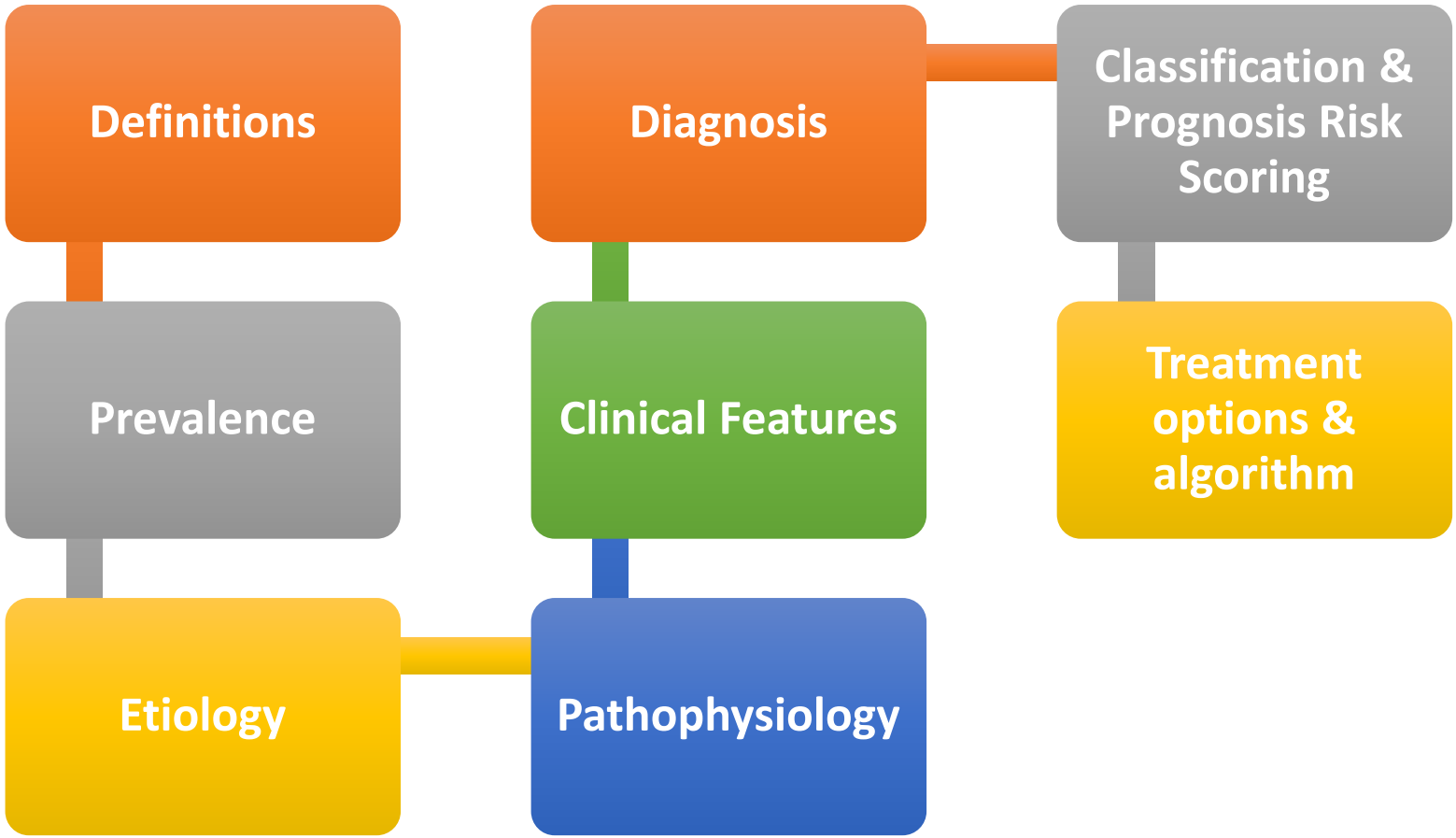
Adrenergic Inhibitors		
Esmolol **(1–2 min, 10–30 min)**	LD 500–1000 mcg/kg IVB over 1 min, then a 50-mcg/kg/min infusion; for additional BP lowering, the bolus dose is repeated, and the infusion is increased in 50-mcg/kg/ min increments as needed to a max 200 mcg/kg/min	Contraindicated in patients with concurrent β-blocker therapy, bradycardia, or decompensated HF AEs: Bronchospasm, HF exacerbation, bradycardia or heart block Caution: May worsen acute HF, asthma (higher doses may block β2-receptors and affect lung function in reactive airway disease), heart block
Labetalol **(5–10 min, 3–6 hr)**	20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to max 3 mg/ kg/hr	Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia
Phentolamine **(2 min, 15–30 min)**	IVB dose 5 mg; additional bolus doses every 10 min as needed	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)


Thank
You!

HEART FAILURE

Dr. Mahmoud Samy, PhD.
Lecturer of Clinical Pharmacy

Floor Plan of This Lecture



HF is a 'BIG' Subject

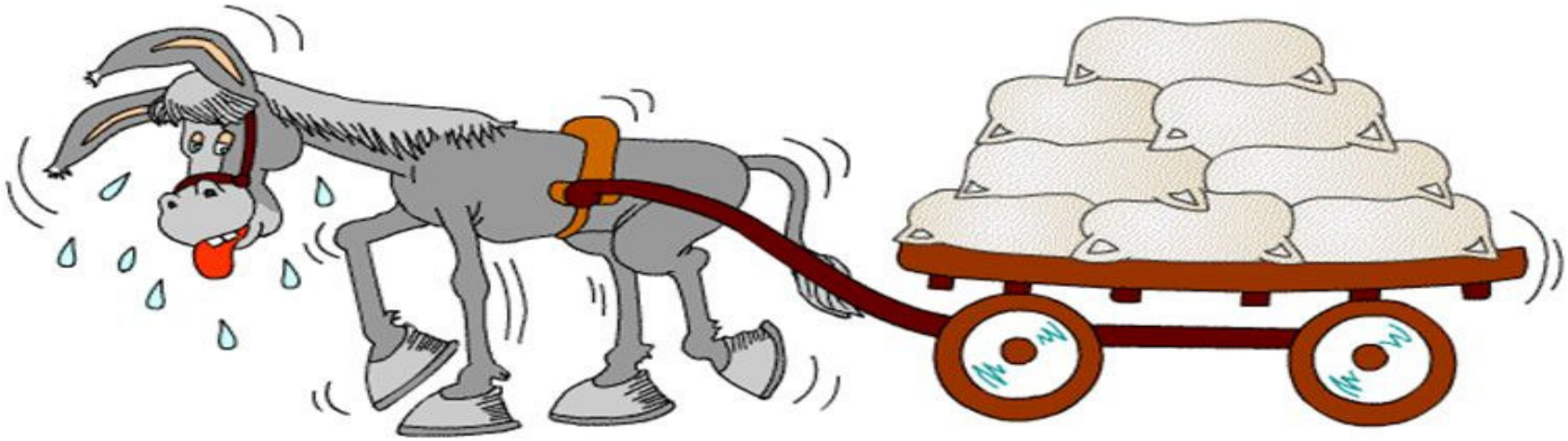
- It afflicts millions of people worldwide
- Has many diverse causes and risk factors
- High mortality; Several drugs and devices
- A paradigm shift in understanding & Rx.
- Extremely costly – huge no. of bed days
- Complicated by many co morbidities
- Truly multidisciplinary in its management

Definitions of HF

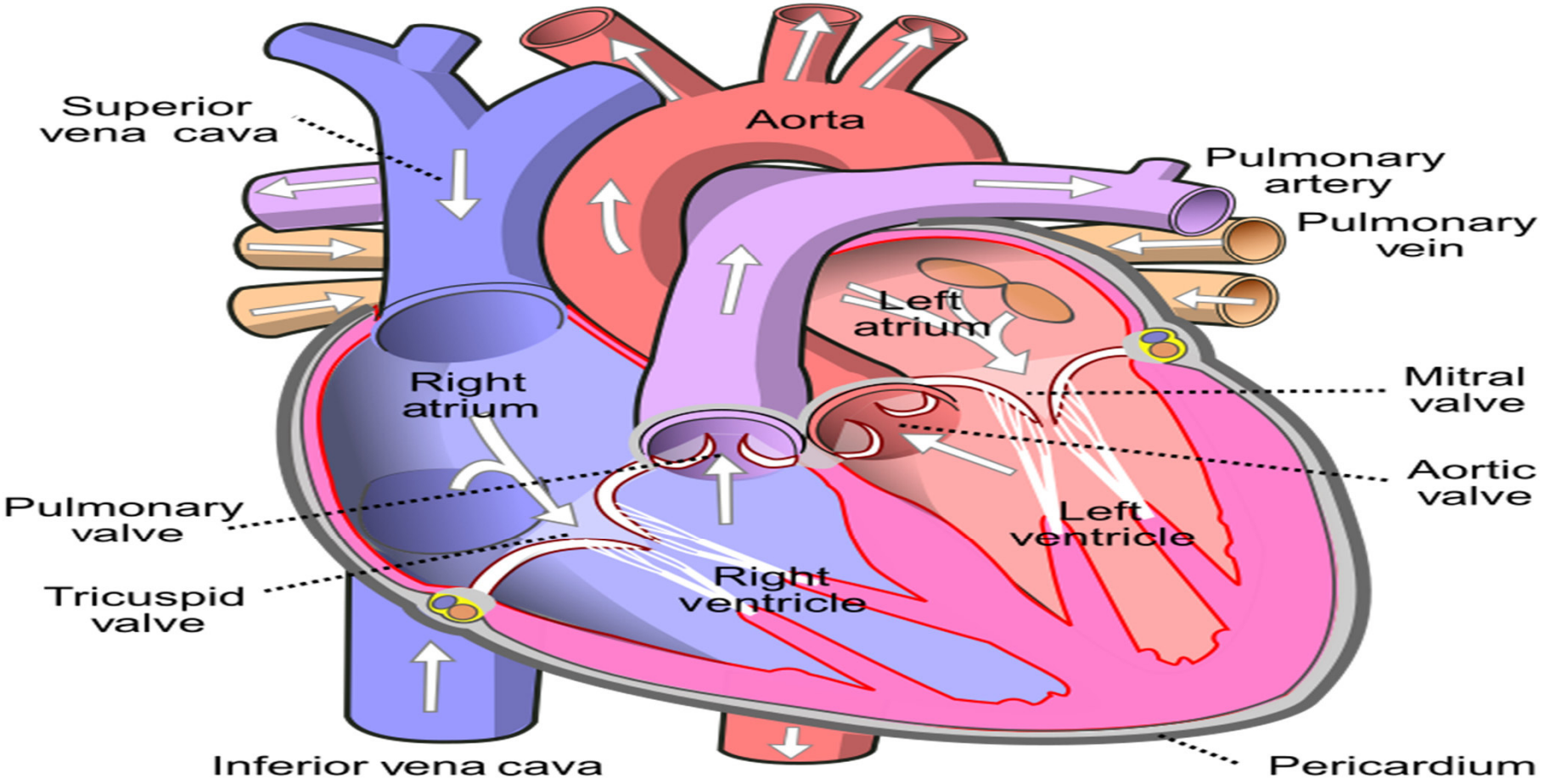
- **A Clinical syndrome that can results from any structural or functional cardiac disorder that impair the ability of the ventricle to fill with or eject the blood**
- **Heart failure characterized by decreased systemic perfusion, inadequate to meet the body's metabolic demands as a result of impaired cardiac pump function.**
- **When the failure is coupled with fluid accumulation in body tissue this called congestive heart failure**

The Donkey Analogy

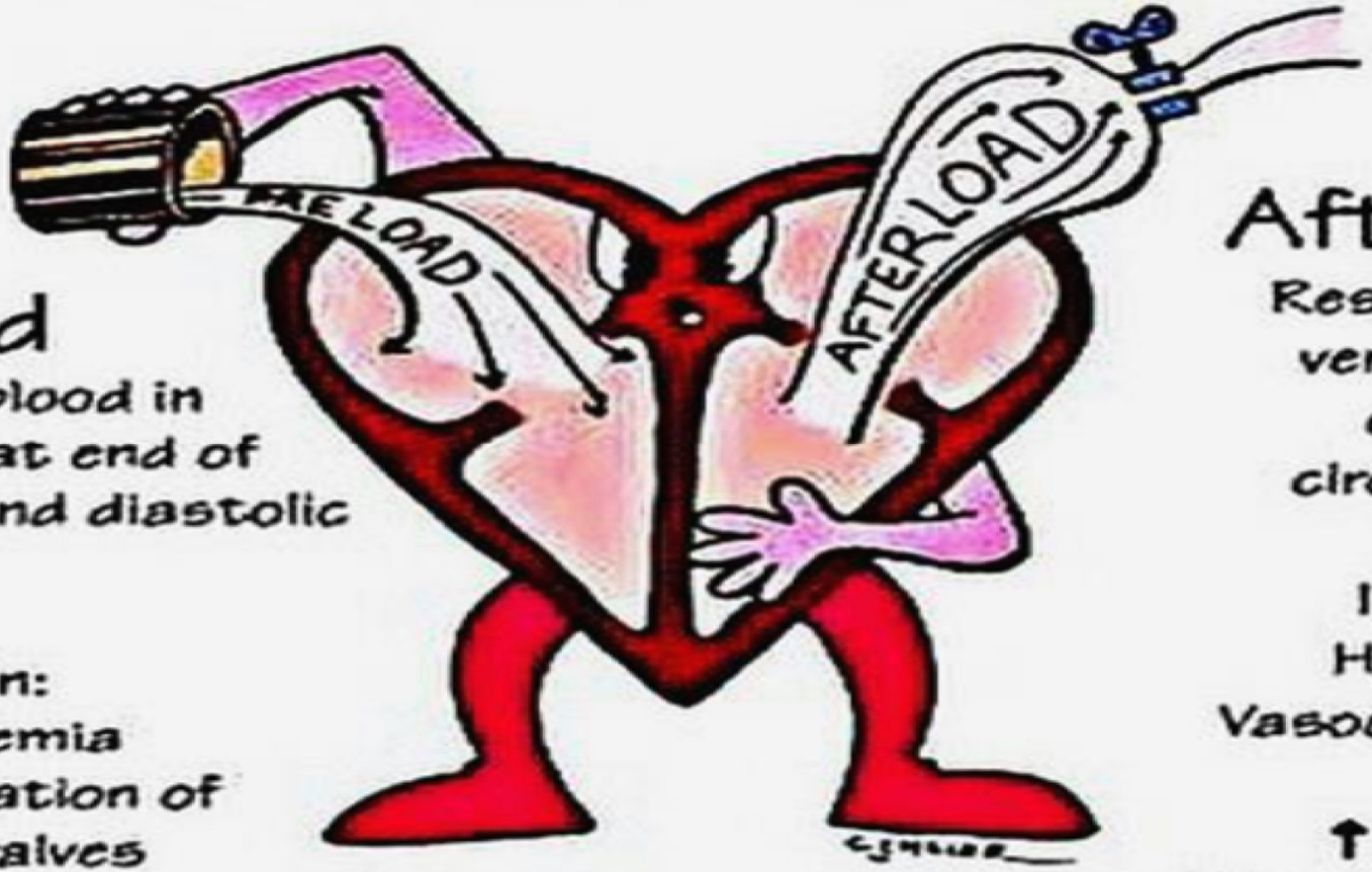
Ventricular dysfunction limits a patient's ability to perform the routine activities of daily living…



Anatomy of the heart



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

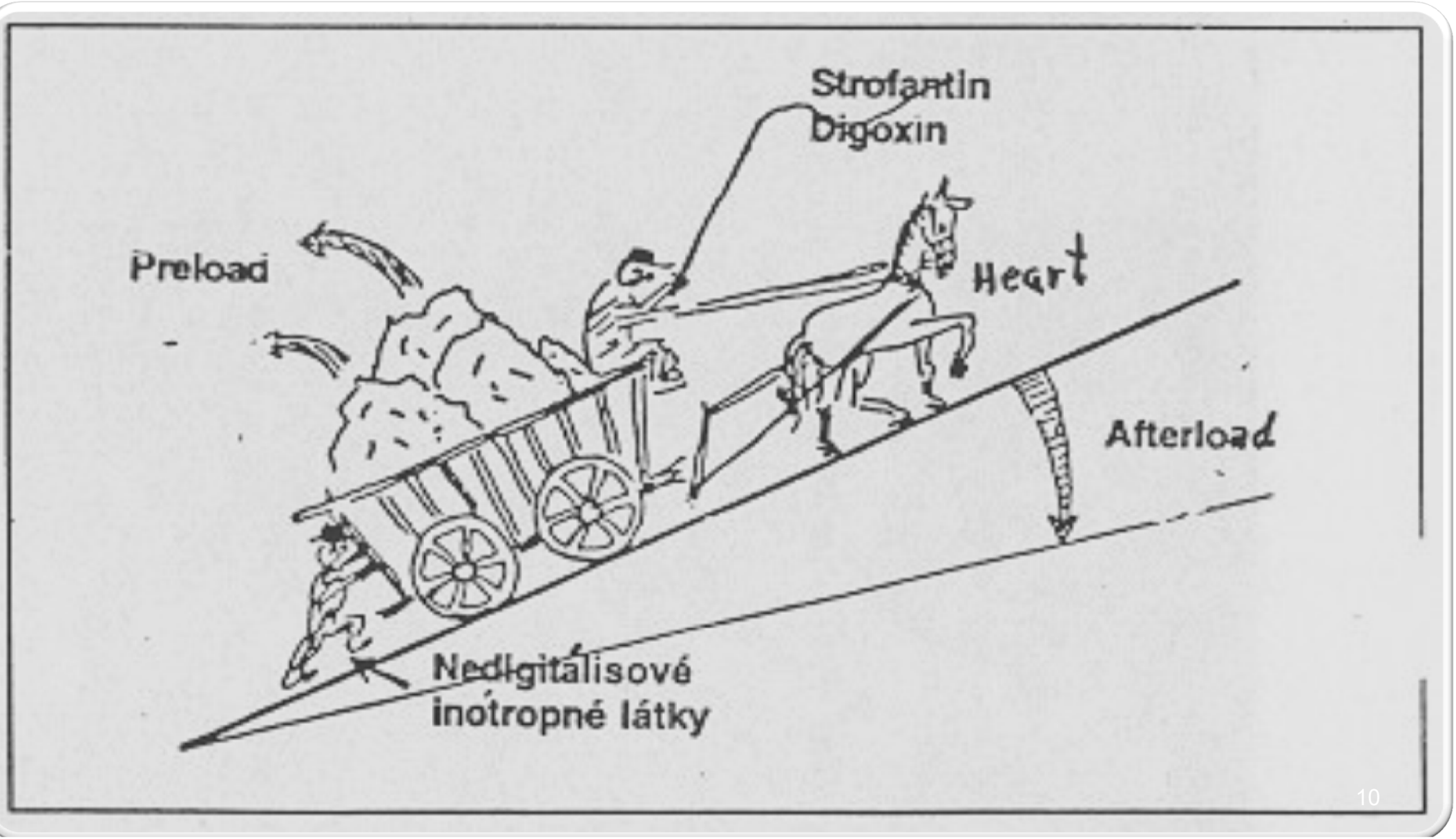
↑ Afterload =
↑ Cardiac workload

Cardiac workload (Key Concepts):

- **Preload describes forces acting on the venous side of the circulation affecting myocardial wall tension.**
- **The volume is maximal when filling finishes at the end of diastole (LV end-diastolic volume).**
- **An increased volume raises the pressure within the ventricle (LV end-diastolic pressure), which in turn increases the "stretch," or wall tension, of the ventricle.**
- **Peripheral venous dilation and decreased peripheral venous volume diminish preload, whereas peripheral venous constriction and increased peripheral venous volume increase preload.**

Cardiac workload (Key Concepts):

- **Afterload is the tension developed in the ventricular wall as contraction (systole) occurs.**
- **This tension is affected by intraventricular pressure, ventricular diameter, and wall thickness.**
- **Afterload is affected by the systemic vascular resistance (SVR) or the impedance against which the ventricle must pump and is estimated by arterial blood pressure (BP).**
- **HTN, atherosclerotic disease, or a narrow aortic valve opening, increases arterial impedance (afterload), thereby increasing the workload of the heart.**


Strofantin
Digoxin
Preload
Heart
Afterload
Nedigitálisové
inotropné látky

Important terms

- **The terms contractility and inotropic state are used synonymously to describe the myocardium's ability to develop force and shorten its fibers independent of preload or afterload. Myocardial contractility is decreased when myocardial fibers are diminished or poorly functioning as may occur in patients with primary cardiomyopathy, valvular heart disease, CAD, or after a myocardial infarction (MI).**
- **Heart Rate: An increased HR is a reflex mechanism to improve CO as ejection fraction (EF) declines. The sympathetic nervous system is the major mediator of this response. The workload and energy demands of a rapid HR ultimately place strain on the heart and can eventually worsen HF.**
- **Positive inotropic (increases contractility), chronotropic (increases heart rate), dromotropic (increases rate of conduction through AV node) and lusitropic (increases relaxation of myocardium during diastole).**

Cardiac Output

CO = SV x HR

- **CO** is cardiac output expressed in L/min
- Normal Cardiac Output is 5 L/min
- **SV** (Stroke Volume) is volume of blood put out/beat
- *Pre load, After load and Contractility* determine the SV
- **HR (Heart rate)** - number of beats/minute (Chronotrop)
- Normally SV = 70 ml/beat. HR = 70/mt; so
- CO = 70 x 70 = 4,900 ml/mt or 5 L approximately

Parameters of LV Function:

- **Fractional shortening (FS):**
- **Is the fraction of any diastolic dimension that is lost in systole. In other words, the percentage of "size reduction" of the left ventricle.**
- **It is End-diastolic dimension (EDD) minus End-systolic dimension (ESD) divided by EDD (times 100 when measured in percentage).**

$$FS = (LVEDD - LVESD / LVEDD) \times 100$$

- **Normal range is 25–45%, Mild is 20–25%, Moderate is 15–20%, and Severe is <15%.**

Parameters of LV Function:

- **Ejection Fraction (EF):**
- One of the measurements used by physicians to assess how well a patient's heart is functioning
- "Ejection" refers to the amount of blood that is pumped out of the heart's main pumping chamber during each heartbeat
- "Fraction" refers to the fact that, even in a healthy heart, some blood always remains within this chamber after each heartbeat
- An ejection fraction is a percentage of the blood within the chamber that is pumped out with every heartbeat
- Normal EF = 50 to 70 percent, May go up to 90% with exercise
- LV Ejection Fraction (EF%): LV EF% = ((LV Diastolic Volume – LV Systolic Volume) / LV Diastolic Volume) X 100

Etiology & Types of Heart Failure

- **Chronic Heart Failure (CHF) & Acute Heart Failure (Cardiogenic Shock)**
- **Low-output versus high-output failure:**

➢**The hallmark of classic low-output HF is a diminished volume of blood being pumped by a weakened heart in patients who have normal metabolic needs.**

➢**In high-output failure, the heart 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, septic shock & pregnancy), the heart becomes exhausted from the increased workload and eventually cannot keep up with demand.**

- **ischemic versus nonischemic heart failure**

Etiology & Types of Heart Failure

- **Left versus right ventricular dysfunction**

➢**Low-output HF is further divided into left and right ventricular dysfunction, or a combination of the two (biventricular failure). Because the left ventricle is the major pumping chamber of the heart, left ventricular dysfunction is the most common form of low-output HF and the major target for pharmacologic intervention. Right ventricular dysfunction may coexist with LV HF if damage is sustained by both sides of the heart or as a delayed complication of progressive left-sided HF.**

- **Systolic versus diastolic dysfunction**

➢**In systolic dysfunction, the stroke volume (SV) (the volume of blood ejected with each contraction; normal, 60– 130 mL) and the subsequent CO (SV × heart rate; normal, 4–7 L/minute) are reduced.**

➢**LV diastolic dysfunction refers to impaired relaxation and increased stiffness of the left ventricle; the EF may or may not be abnormal, and the patient may or may not be symptomatic.**

Prevalence or Epidemiology of HF

- Clinical criteria – Prevalence 1-2 %
- Males > Females; in 65+ Prevalence 7%
- 50% of LVSD is asymptomatic
- NEF HF varies from 15 to 50%
- Incidence 0.2 to 0.3 %; ↑ with age

Pathophysiology of Heart Failure

- **A. Sympathetic Nervous System**

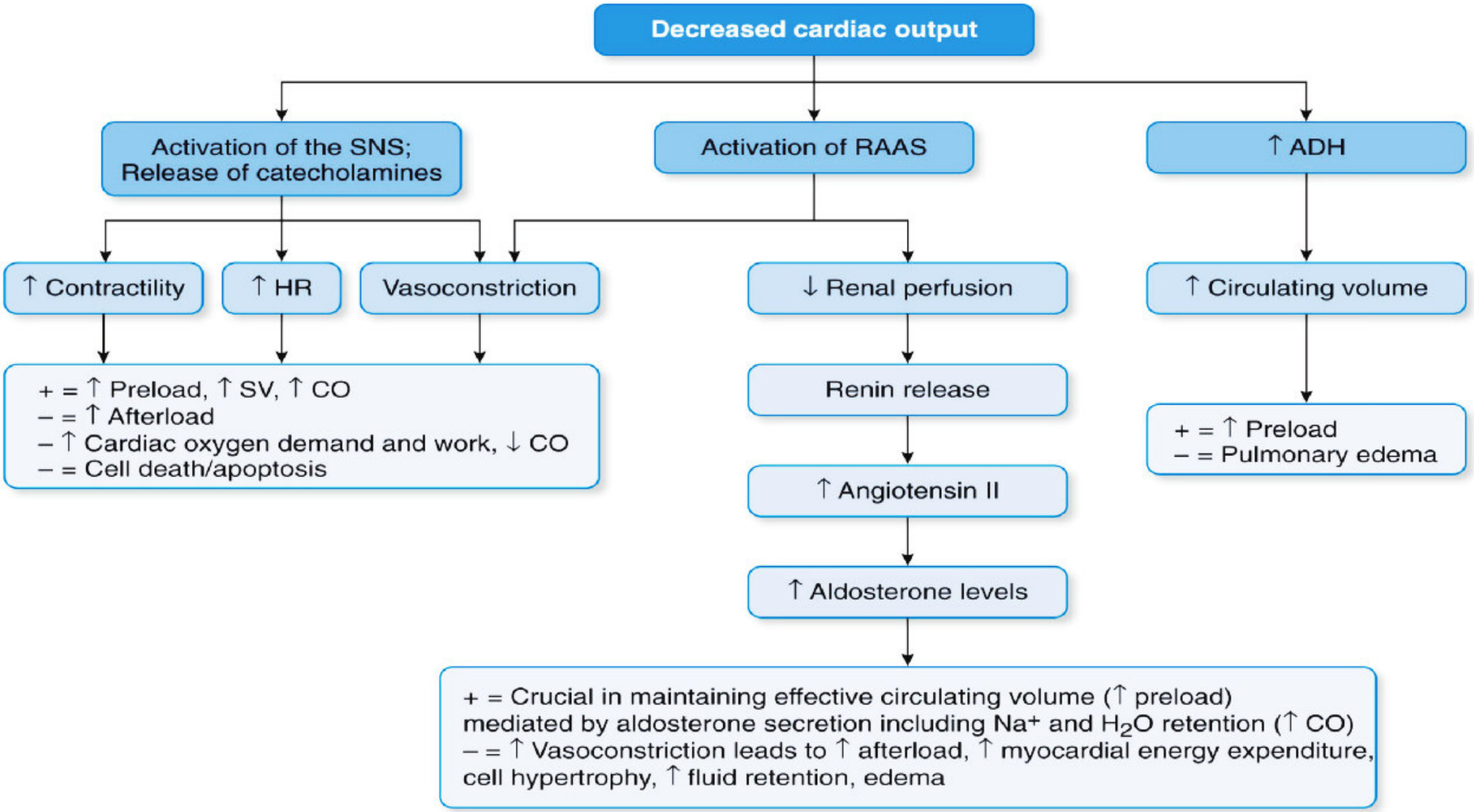
⬇CO activates baroreceptors - ⬆ SNS

Effects of ⬆ Circulating Epinephrine & NE

- Increased Heart Rate
- Increased Blood Pressure
- Increased myocardial oxygen demand
- Toxic effects on myocardium – cell death
- Down regulation of β_1 receptors in heart
- Decrease in parasympathetic activity

Pathophysiology of Heart Failure

- B. Homeostatic Compensatory Mechanisms
- Activation of Sympathetic Nervous System (First line)
- In vascular system resulting in vasoconstriction (What effect on afterload?)
- Kidneys: renal function and the renin–angiotensin–aldosterone System
- The reduced CO in HF leads to the stimulation angiotensin II, which is a potent vasoconstrictor. Angiotensin II is also a potent stimulator of the sympathetic nervous system, which increases SVR. Renal vascular resistance is increased, and the glomerular filtration rate (GFR) is decreased. As the GFR decreases, more sodium and water are reabsorbed.
- A diminished effective circulating plasma volume and angiotensin II also stimulate release of antidiuretic hormone (ADH) from the pituitary, resulting in the retention of free water in the collecting ducts.
- Liver : Stores venous volume causing ascites, hepatomegaly


Decreased cardiac output
Activation of the SNS; Release of catecholamines
Activation of RAAS
↑ ADH
↑ Contractility
↑ HR
Vasoconstriction
↓ Renal perfusion
↑ Circulating volume
+ = ↑ Preload, ↑ SV, ↑ CO
– = ↑ Afterload
– ↑ Cardiac oxygen demand and work, ↓ CO
– = Cell death/apoptosis
Renin release
↑ Angiotensin II
↑ Aldosterone levels
+ = ↑ Preload
– = Pulmonary edema
+ = Crucial in maintaining effective circulating volume (↑ preload) mediated by aldosterone secretion including Na^+ and H_2O retention (↑ CO)
– = ↑ Vasoconstriction leads to ↑ afterload, ↑ myocardial energy expenditure, cell hypertrophy, ↑ fluid retention, edema

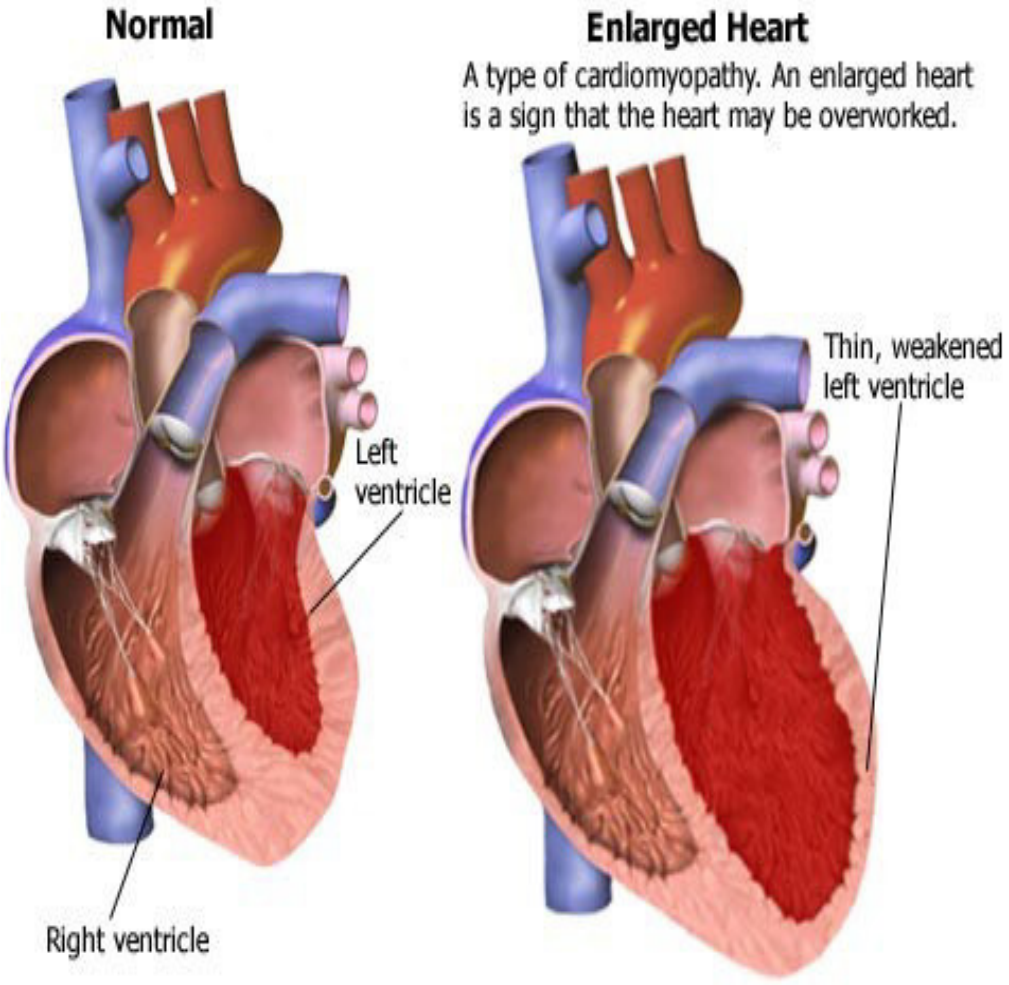
Pathophysiology of Heart Failure

- **C. Other hormonal mediators**
- **Endothelin-1 (ET-1):** Serum concentrations of ET-1 are elevated in HF, pulmonary HTN, MI, ischemia, and shock, and **cause vasoconstriction, potentiation of cardiac remodeling, and decreased renal blood flow (RBF).**
- **Natriuretic peptides (NPs): A-type natriuretic peptide**, previously referred to as atrial natriuretic peptide or atrial natriuretic factor, is secreted by the atria in response to dilatation. Similarly, **B-type natriuretic peptide** (BNP) is produced by the ventricular myocardium in response to elevations of end-diastolic pressure and volume. **Type-C natriuretic peptide (CNP)** is secreted by lung, kidney, and vascular endothelium in response to shear stress.
- The NPs are considered to be a favorable form of neurohormonal activation. **Among their positive attributes are antagonism of the renin–angiotensin system, inhibition of sympathetic outflow, and ET-1 antagonism. The net effect is peripheral and coronary vasodilation decreasing preload and afterload.**

Pathophysiology of Heart Failure

- **C. Other hormonal mediators**
- **The BNP precursor is cleaved to produce the biologically active C-terminal fragment (BNP) and an inactive N-terminal fragment (NT-proBNP). Plasma level measurement of either BNP or NT-proBNP can be used as a biologic marker to differentiate HF-induced dyspnea from other causes of respiratory distress. BNP levels less than 100 pg/mL usually indicate absence of HF, whereas levels greater than 400 pg/mL are highly indicative of HF.**
- Inflammatory Cytokines, Interleukins, Tissue Necrosis Factor, Prostacyclin, and Nitric Oxide

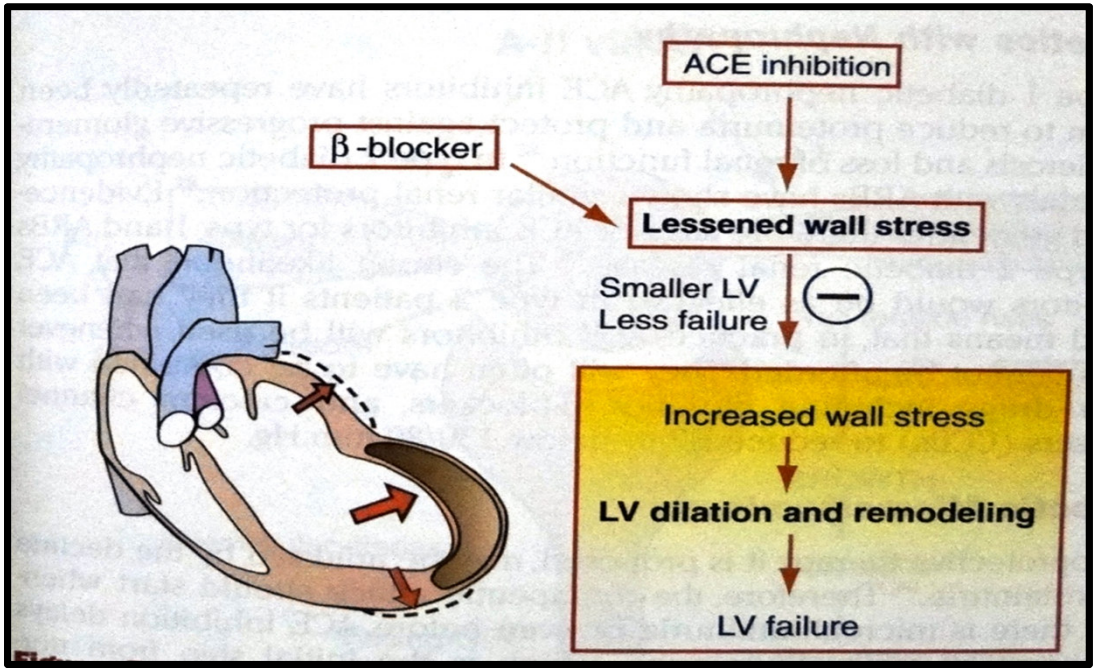
D. Cardiac Remodeling



Na and H_2O retention, ↓ Performance

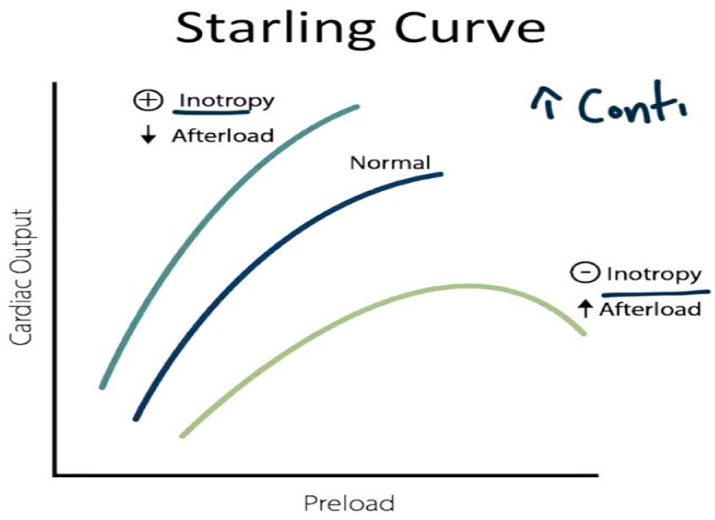
Myocyte hypertrophy, death, fibrosis

Dilated and spherical ventricle, thinned



Frank–Starling Curve

- **Demonstrates a curvilinear relationship between LV myocardial muscle fiber "stretch" (wall tension) and myocardial work. As stretch increases, the volume of blood ejected (SV) with each contraction increases.**
- **Dilatation of the ventricles initially may serve as an effective compensating mechanism in systolic failure, but becomes inadequate as the elastic limits of the muscle fibers are reached.**



HFrEF or Systolic dysfunction

- **Defined as a clinical diagnosis of HF and an LVEF of 40% or less**
- **Dilated ventricle**
- **Two thirds of cases are attributable to coronary heart disease (CHD).**
- **One third of cases are attributable to nonischemic cardiomyopathy: HTN, Thyroid disease, Obesity, Stress, Myocarditis, Idiopathic, Tachycardia, Peripartum**
- **Cardiotoxins**

➢**Alcohol & Cocaine**

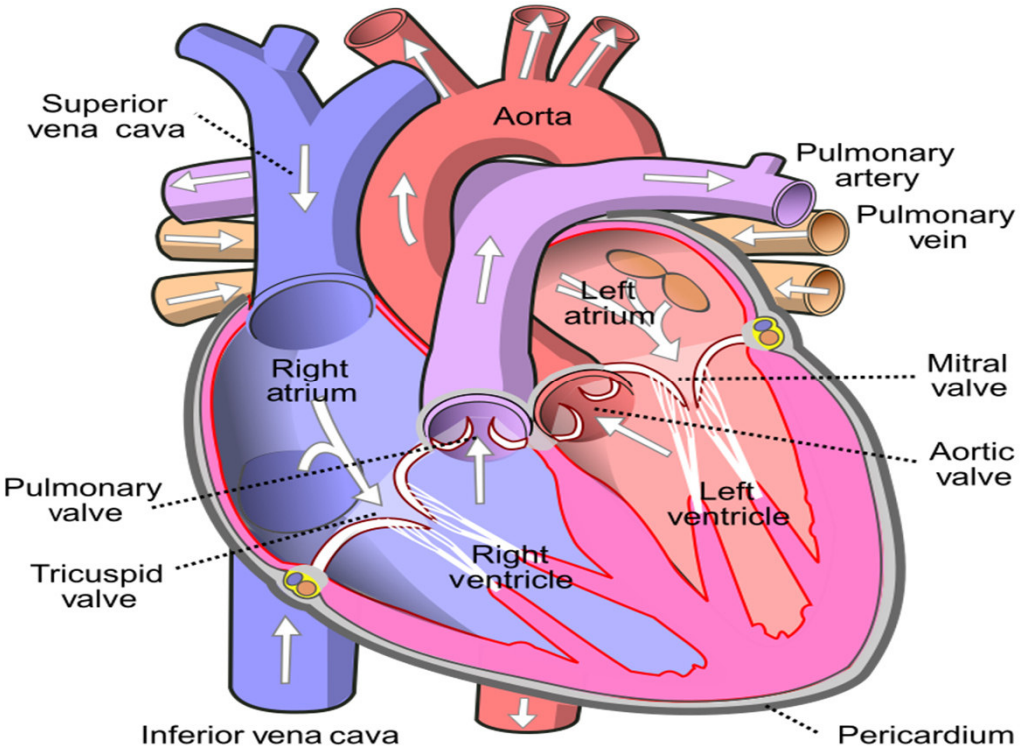
➢**Chemotherapeutic agents: NSAIDS, Anthracyclines, Cyclophosphamide (high dose), Fluorouracil, Trastuzumab/pertuzumab & Mitoxantrone**

HFpEF or Diastolic dysfunction

- **Defined as an LVEF of 50% or greater; borderline HFpEF is LVEF 41%–49%**
- **Accounts for about 50% (highly variable) of patients with HF**
- **Impaired ventricular relaxation and filling**
- **Normal wall motion**
- **Most common cause is HTN (60%–89%).**

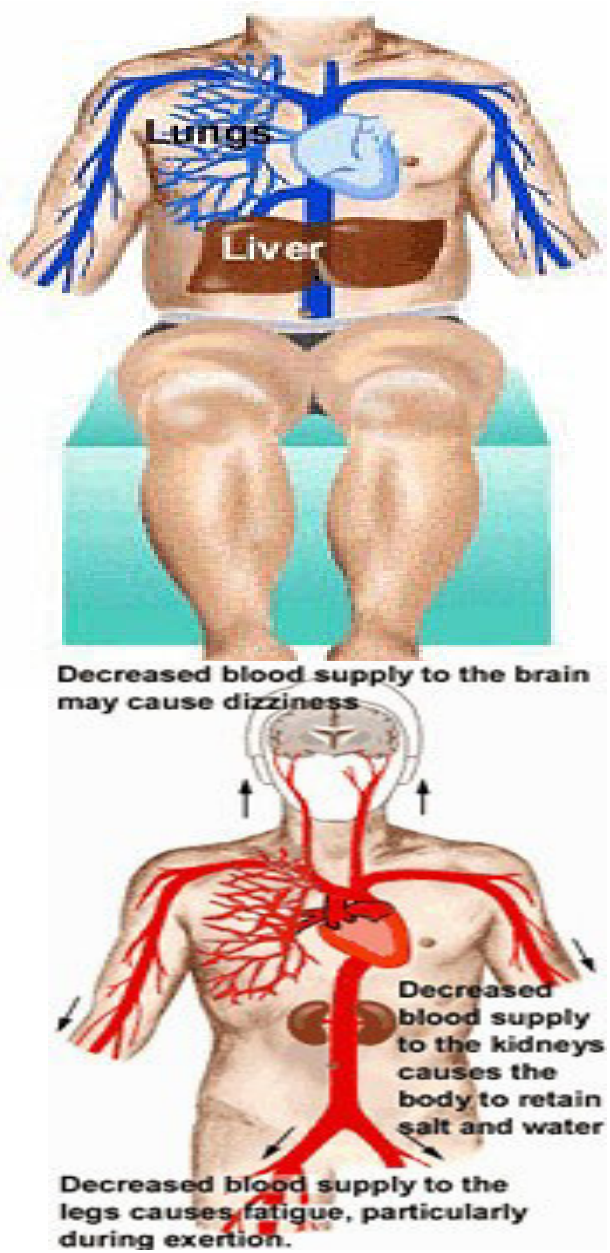
Clinical Manifestations

- **Pulmonary effects**
  - Pulmonary edema
  - Dyspnea
  - Paroxysmal nocturnal dyspnea (PND)
  - Orthopnea
  - Dyspnea on exertion
  - Pleural effusion
- **Cardiac effects**
  - Cardiomegaly
  - Tachycardia
  - S 3 gallop (A S3 can be a normal finding in children (Anemia), pregnant females and well-trained athletes).. **lub-dub-ta**

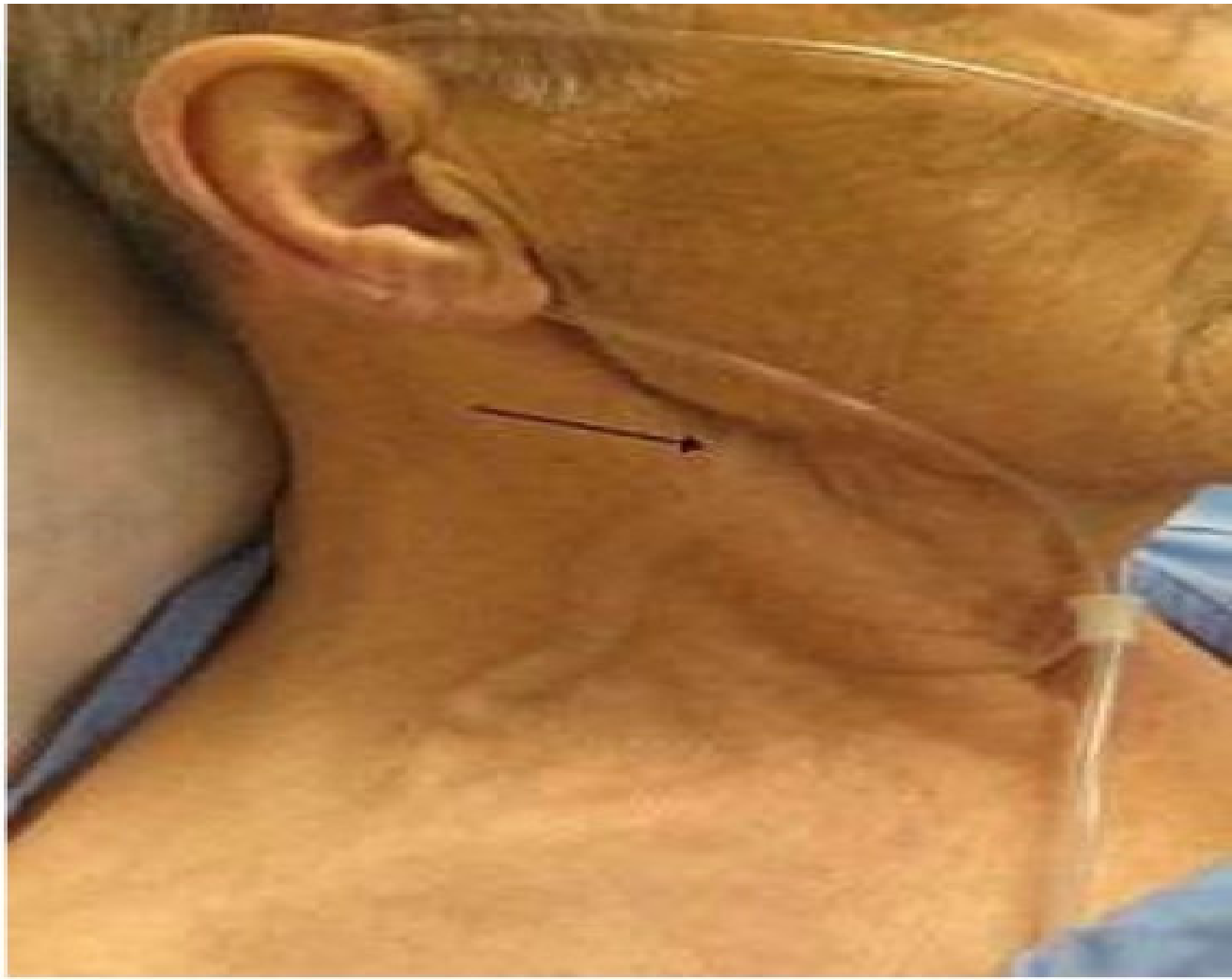


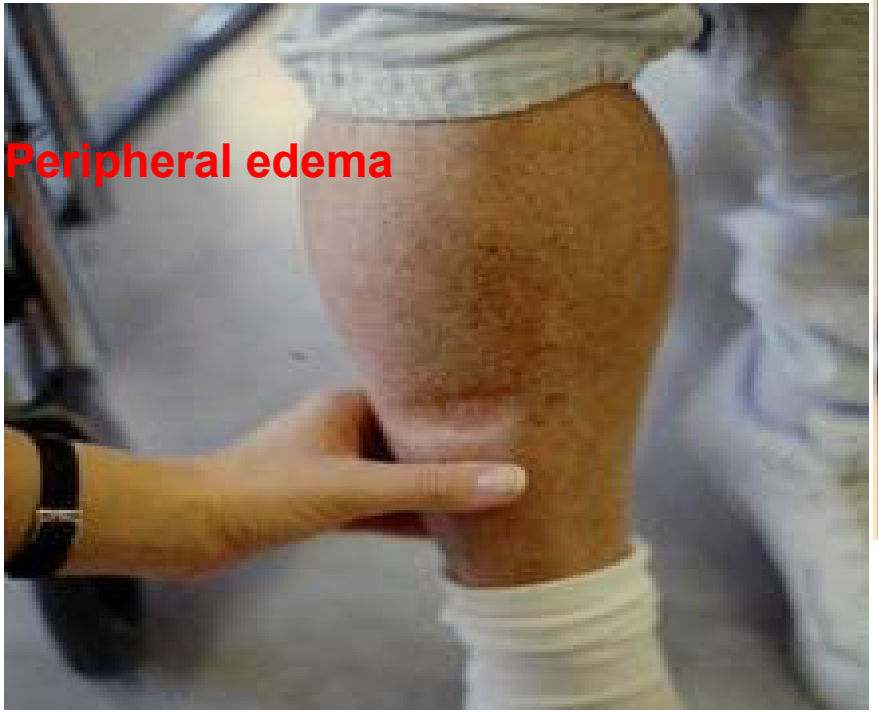
Clinical Manifestation

- Systemic effects
- Hepatic congestion
- Jugular vein distention (JAD)
- Ascites
- Peripheral edema
- Splenomegaly and abdominal pain
- Anorexia and weight loss
- Weakness and fatigue
- Cyanosis
- Oliguria /Nocturia



A man with severe congestive cardiac failure with marked jugular venous distension. **External jugular vein marked by arrow.**





HF Classification

ACC/AHA Stage		NYHA Functional Class	
A	At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HF symptoms
		II	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
		IV	Symptoms of HF at rest or unable to carry out any physical activity
D	Refractory HF requiring specialized interventions	IV	Symptoms of HF at rest

HF Classification

ACC/AHA Stage		NYHA Functional Class	
A	At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I (Mild) 	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	II (Mild) 	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III (Moderate) 	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
D	Refractory HF requiring specialized interventions	IV (Severe) 	Symptoms of HF at rest or unable to carry out any physical activity

Diagnostic Tests

- **Doppler Echocardiogram or Radionuclide ventriculography (Technetium-99m (99mTc) to assess ejection fraction (EF & FS)**
- **Chest X-ray**
- **ECG**
- **Cardiac stress test**
- **Cardiac catheterization**
- **Cardiac computed tomography scan or magnetic resonance imaging**
- **Pulmonary function tests**
- **CBC : Since anemia can exacerbate heart failure**
- **Serum electrolytes and creatinine before starting high dose diuretics**
- **Fasting Blood glucose: To evaluate for possible diabetes mellitus**
- **Thyroid function tests: Since thyrotoxicosis can result in A. Fib, and hypothyroidism can results in HF.**
- **Iron studies: To screen for hereditary hemochromatosis as cause of heart failure.**
- **ANA: To evaluate for possible lupus**
- **Viral studies: If viral myocarditis suspected.**

Goals of therapy

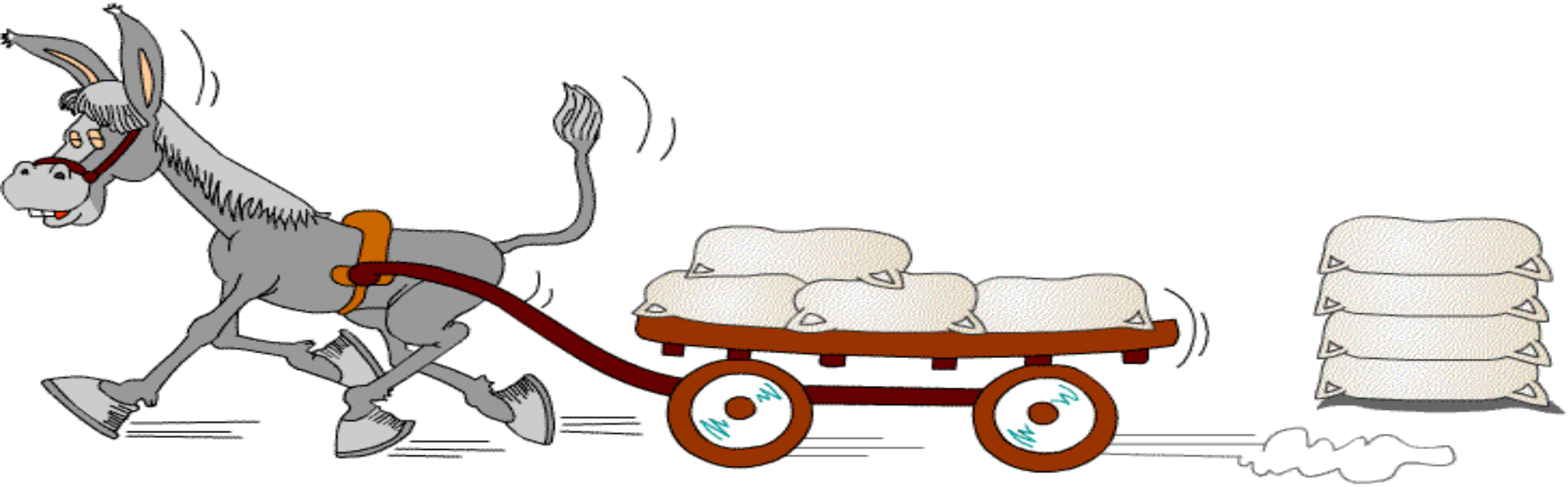
- **Modify or control risk factors (e.g., HTN, obesity, DM)**
- **Manage structural heart disease**
- **Reduce morbidity and mortality**
- **Prevent or minimize Na and water retention**
- **Eliminate or minimize HF symptoms** (complaints of SOB and PND, improve sleep quality, and increase exercise tolerance)
- **Block compensatory neurohormonal activation caused by reduced cardiac output (CO)**
- **Slow progression of worsening cardiac function.**

HF*r*EF Pharmacologic therapy

- **a. Diuretics**
- **Place in therapy**: Indicated in patients with evidence of fluid retention (class I indication)
- Short-term benefit (days)
- (a) Decreased jugular venous distension
- (b) Decreased pulmonary congestion
- (c) Decreased peripheral edema
- Intermediate-term benefits (weeks to months)
- (d) Decreased daily symptoms
- (e) Increased exercise tolerance
- **Long-term benefits (months to years): No benefit on mortality**

Diuretics

Reduce the number of sacks on the wagon



Diuretics

- **Should be combined with ACE) inhibitor, β-blocker, and aldosterone receptor antagonist**
- **Start with a low initial dose and then double the dose and titrate according to the patient's weight as needed.**
- **If a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day (may be more aggressive in the inpatient setting).**
- **Long-term therapy should be adjusted to maintain a euvolemic state.**
- **A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed.**
- **Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function.**
- **Monitoring: Monitor and replace K and magnesium as needed, especially with loop diuretics (goal with cardiovascular [CV] disease is K of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor SCr and BUN to avoid acute kidney injury with overdiureses. Also monitor HCO3 for metabolic alkalosis with overdiuresis.**

Diuretics and Recommended Dosing

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide	10–67	20–40 mg daily or BID	600	6–8
Bumetanide	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid	100	25–50 mg daily or BID	200	6–8
Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)				
Hydrochlorothiazide	65–75	25 mg daily or BID	100	6–12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide	30–50	250–500 daily or BID	2000	6–12

ACE inhibitors

- **Place in therapy: Recommended in all patients with HFrEF and current or prior symptoms, unless contraindicated (class I indication)**
- **Benefits**

(a) Decreased mortality

(b) Decreased hospitalizations

(c) Symptom improvement - Improved clinical status - Improved sense of well-being

- **Mechanism of action**
- **(a) Blocks production of angiotensin II**

➢ **Decreases sympathetic stimulation**

➢ **Decreases production of aldosterone and vasopressin**

➢ **Decreases vasoconstriction (afterload and preload)**

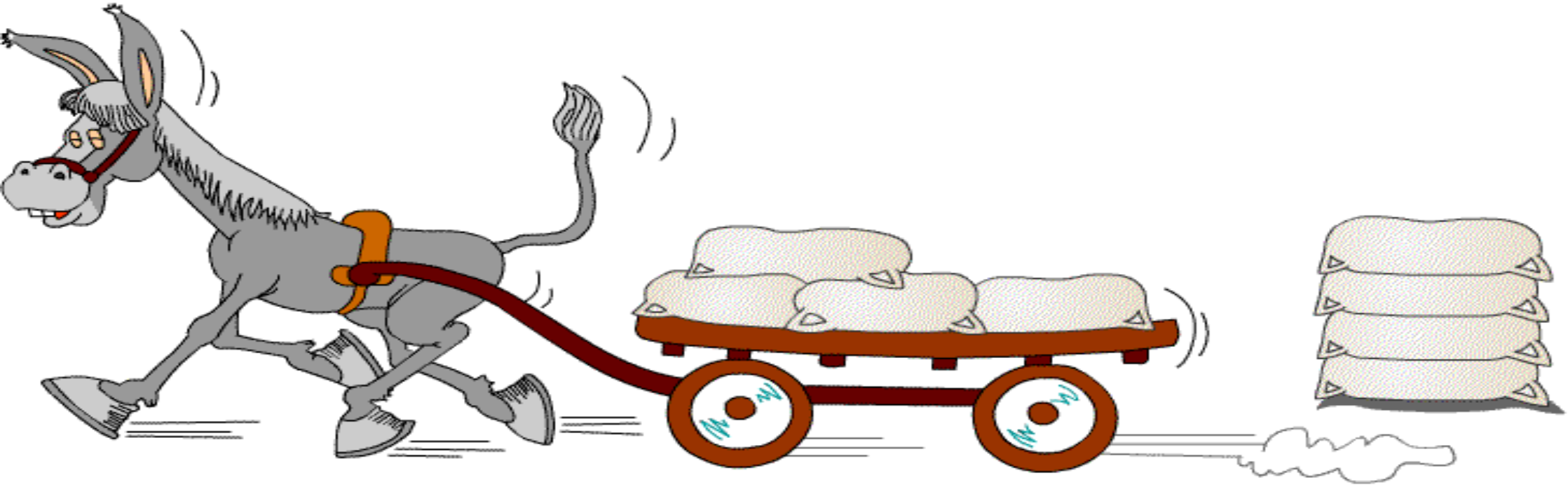
- **(b) Increases bradykinins (decreases their metabolism)**

➢ **Increases vasodilatory prostaglandins (NSAIDs antagonize this effect)**

➢ **May attenuate myocardial remodeling**

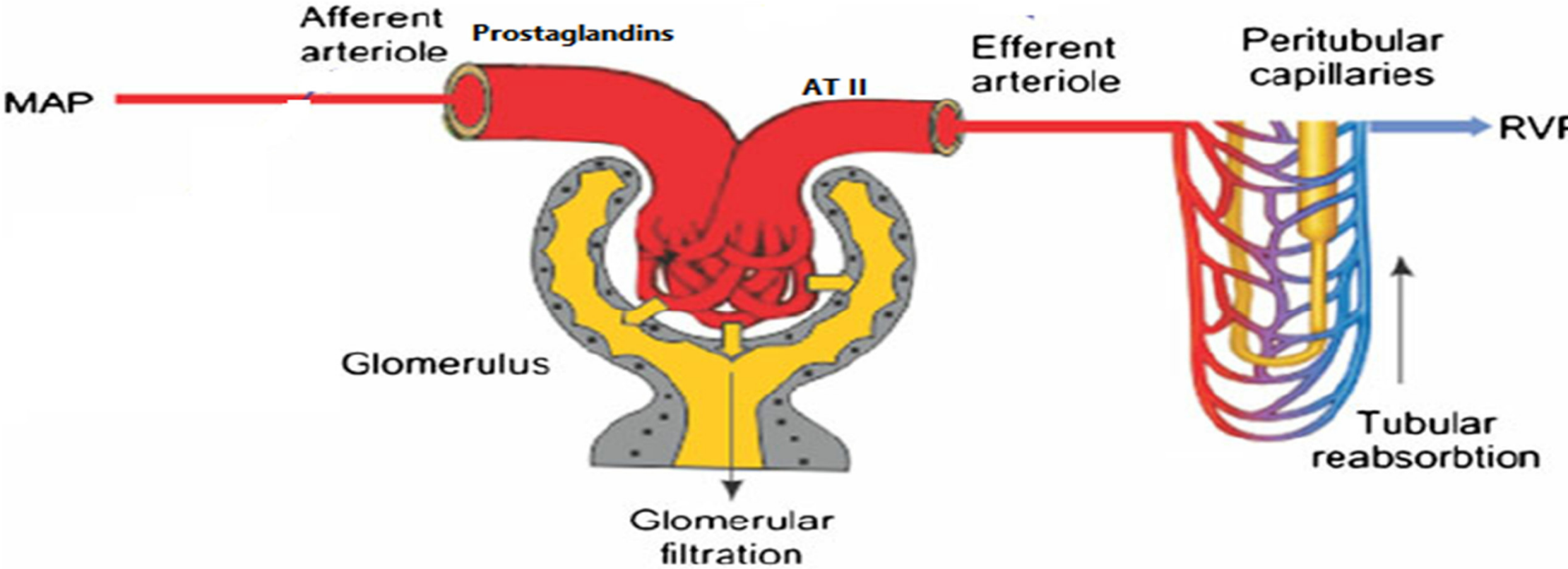
ACE Inhibitors

Reduce the number of sacks on the wagon



ACE inhibitors

- **Dosing and administration considerations**
  - **Start low and double the dose every 1–4 weeks to target dose.**
  - **Patients may notice improvement in symptoms in several weeks.**
  - **Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.**
- **Monitoring**
  - **Monitor SCr and K for 1–2 weeks after initiating therapy.**
  - **SCr may rise (up to a 30% increase is acceptable).**
  - **Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted.**
  - **Patients with risk factors such as preexisting renal insufficiency or concomitant treatment with NSAIDs or high-dose diuretics may require more frequent monitoring.**
  - **Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).**
  - **Symptoms of hypotension are often not present with small dose increases.**
  - **Angioedema: ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate**



Predominant afferent vasodilation: RBF ↑ ; GFR ↑
Predominant efferent vasodilation: RBF ↑ ; GFR ↓
Afferent + efferent vasodilation: RBF ↑ ↑ ; GFR ↑ ↓

Angiotensin receptor blockers

- **Place in therapy**
- **Recommended in patients with HFrEF with current or prior symptoms who are unable to take an ACE inhibitor (class I indication). Have not been proven superior to ACE inhibitors at target HF dosages.**
- **Benefits**
- **Decreased HF-related hospitalizations and decreased death from CV causes.**
- **Mechanism of action**

➢ **Selectively block the binding of angiotensin II to the angiotensin I receptor**

➢ **Deters vasoconstriction and aldosterone-secreting effects**

➢ **Does not affect ACE or inhibit kinin catabolism**

- **Dosing and administration**
- **Monitoring**

β-blockers

- **Place in therapy: Recommended in all patients with HFrEF with current or prior symptoms unless contraindicated (class I indication)**
- **Benefits (when added to an ACE inhibitor)**

➢ **Decreased mortality - Decreased hospitalizations - Symptom improvement- Improved clinical status**

- **Mechanism of action**
- **(a) Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system**

✓ **Decreases ventricular arrhythmias (sudden cardiac death)**

✓ **Decreases cardiac hypertrophy and cardiac cell death**

✓ **Decreases vasoconstriction and HR**

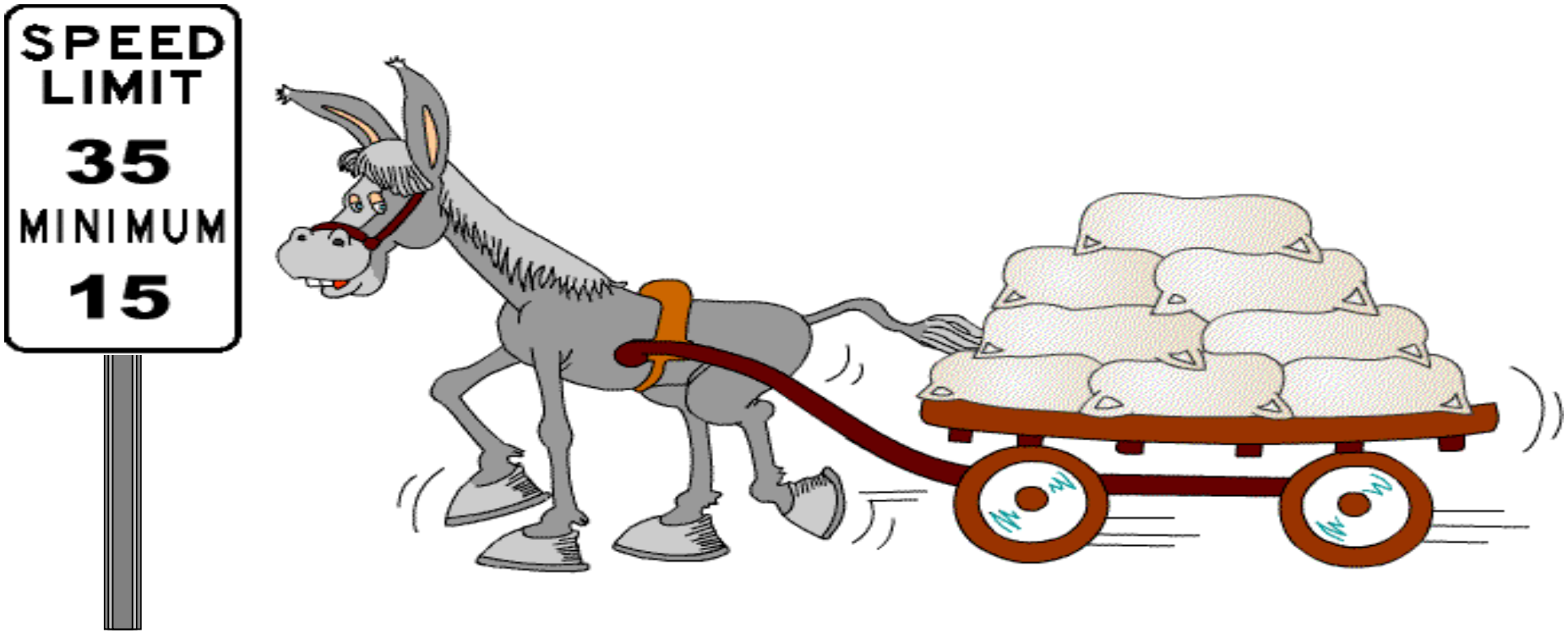
- **(b) Carvedilol also provides α1-blockade.**

✓ **Further decreases SVR (afterload)**

✓ **Results in greater reduction in BP than metoprolol succinate**

Beta-Blockers

- Limit the donkey's speed, thus saving energy



β-blockers

- Dosing and administration considerations
- **Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HFrEF.**
- Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvolemic.
- Should not be prescribed without diuretics in patients with current or recent history of fluid retention.
- Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose. Aim to achieve target dose in 8–12 weeks.
- Avoid abrupt discontinuation; can precipitate clinical deterioration
- Might not notice improvement in symptoms for several months
- Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily 50 mg twice daily if weight > 85 kg.
Carvedilol CR	10 mg daily	80 mg daily
Metoprolol succinate	12.5–25 mg daily	200 mg daily

β-blockers

- **Monitoring**

❖**BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)**

✓ **If these symptoms appear, lower the dose by 50%.**

✓**Of importance, remember that higher β-blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first or scheduling one agent at bedtime and one in the morning.**

❖**Increased edema or fluid retention (monitor in 1–2 weeks)**

❖**Do not increase β-blocker dose if patient develops fluid retention during therapy initiation or titration**

❖**Fatigue or weakness**

✓**Usually resolves spontaneously in several weeks**

✓**May require dosage decrease or discontinuation**

Aldosterone receptor antagonists (ARAs)

- **Place in therapy**
- **Recommended in patients with NYHA class II–IV with an LVEF of 35% or less.**
- **Patients with NYHA class II should have a history of CV hospitalization or elevated B-type natriuretic peptide (BNP) levels (class I indication).**
- **Recommended to reduce morbidity and mortality in patients after a myocardial infarction (MI) when they have an LVEF less than or equal to 40% with symptoms of HF or an LVEF less than 40% and DM (class I indication).**
- **Benefits of ARA in NYHA class III and IV HF**
- **Decreased mortality - Decreased hospitalizations - Improved symptoms**
- **Mechanism of action**
- **Blocks effects of aldosterone in the kidneys, heart, and vasculature**
- **Decreases K and magnesium loss; decreases ventricular arrhythmias**
- **Decreases Na retention; decreases fluid retention**
- **Eliminates catecholamine potentiation; decreases BP**
- **Blocks direct fibrotic actions on the myocardium**

ARAs

- Dosing and administration considerations
- Should be added to ACE inhibitor (or ARB) and β-blocker therapy
- SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women (or estimated glomerular filtration rate greater than 30 mL/minute/1.73 m2), and K should be less than or equal to 5.0 mEq/L.
- In the absence of hypokalemia (K less than 3.5 mEq/L), supplemental K is not recommended when taking an ARA.
- Monitoring
- K and SCr within 2–3 days, again at 7 days after starting therapy, monthly for first 3 months, and every 3 months thereafter. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
- Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
- Gynecomastia (spironolactone)
- Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

	eGFR ≥ 50 mL/min/1.73 m2		eGFR 30-49 mL/min/1.73 m2	
	Initial dose	Maintenance dose	Initial dose	Maintenance dose
Eplerenone	25 mg daily	50 mg daily	25 mg every other day	25 mg daily
Spironolactone	12.5–25 mg daily	25 mg daily or BID	12.5 mg daily or every other day	12.5–25 mg daily

Digoxin

- **Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIa indication) or congestive heart failure, HF With atrial fibrillation or Paroxysmal supraventricular tachycardia ; should be added after ACE inhibitor (or ARB) and β-blocker therapy**
- **Benefits**
- **Improved symptoms - Improved exercise tolerance - Decreased hospitalizations**
- **No effect on mortality**
- **Mechanism of action (in HF)**
- **Inhibits myocardial Na-K adenosine triphosphatase (Na+/K+ ATPase),**
- **Enhances inotropy of cardiac muscle, ↑force of contraction & Cardiac Output**
- **Negative chronotropic effect, ↓ Heart rate**
- **Decreases central sympathetic outflow by sensitizing cardiac baroreceptors**
- **Decreases renal reabsorption of Na**

Digoxin

Mechanism of the +ve inotropic action:

In therapeutic dose leads to partial inhibition of Na^+/K^+ ATPase enzyme

Normally

intracellular Na^+ resulting in:

Force Of Contractility

Digoxin

Like the carrot placed in front of the donkey

Digoxin

- **Dosing and administration considerations**
- **For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.**
- **Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.**
- **Time of digitalization 5-7 days, duration of action 2- 6 days, t1/2 40 hrs, bioavailability 60-80%, onset of action 15-30 minutes.**
- **Avoid abrupt discontinuation; can precipitate clinical deterioration**
- **Drug interactions: Digoxin concentrations are increased with concomitant:**
- **Clarithromycin, erythromycin**
- **Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency) & Dronedarone (reduce digoxin dose by 50%)**
- **Itraconazole, posaconazole**
- **Cyclosporine, tacrolimus**
- **Verapamil**
- (The p-gp drug efflux transporter **mechanism)**

Digoxin

- **Monitoring**
- **Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.**
- **Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.**
- **Risk of toxicity increases with age and renal impairment.**
- **Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.**
- **Signs of toxicity generally include nausea, vomiting, vision changes.**
- **SCr should be monitored because the drug is primarily cleared renally.**
- **Digoxin toxicity treatment:**
- **Oral or parenteral potassium supplements**
- **Digoxin antibody (digibind) is used specifically to treat life-threatening digoxin overdose.**
- **For ventricular arrhythmias: Lidocaine IV drug of choice.**
- **For supraventricular arrhythmia: Propranolol may be given IV or orally**
- **For AV block and bradycardia :Atropine 0.6 -1.2 mg IM**

Property	Digoxin	Digitoxin
Oral absorption	60 -80 %	90 -100 %
Plasma protein binding	25 %	95%
Onset of action	15 -30 min	½ to 1 hour
Duration of action	2-6 days	2-3 weeks
Plasma t ½	40 hrs	5-7 days
Route of elimination	Renal excretion	Hepatic metabolism
Time for digitalization	5-7 days	25-30 days
Daily maintainence dose	0.125 – 0.5 mg	0.05 -0.2 mg
Administration	Oral / IV	Oral

Vasodilators: Hydralazine/isosorbide dinitrate

- **Place in therapy**
- **Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for African American with patients with NYHA class III or IV HFrEF (class I indication)**
- **May be useful in patients with current or prior symptoms of HFrEF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)**
- **Benefits**
- **Decreased mortality**
- **Reduced pulmonary congestion and improved exercise tolerance**
- **Mechanism of action**
- **(a) Hydralazine: Arterial vasodilator (reduces afterload) & Increases effect of nitrates through antioxidant mechanisms**
- **(b) Isosorbide dinitrate: Stimulates nitric acid signaling in the endothelium & Venous vasodilator (reduces preload)**

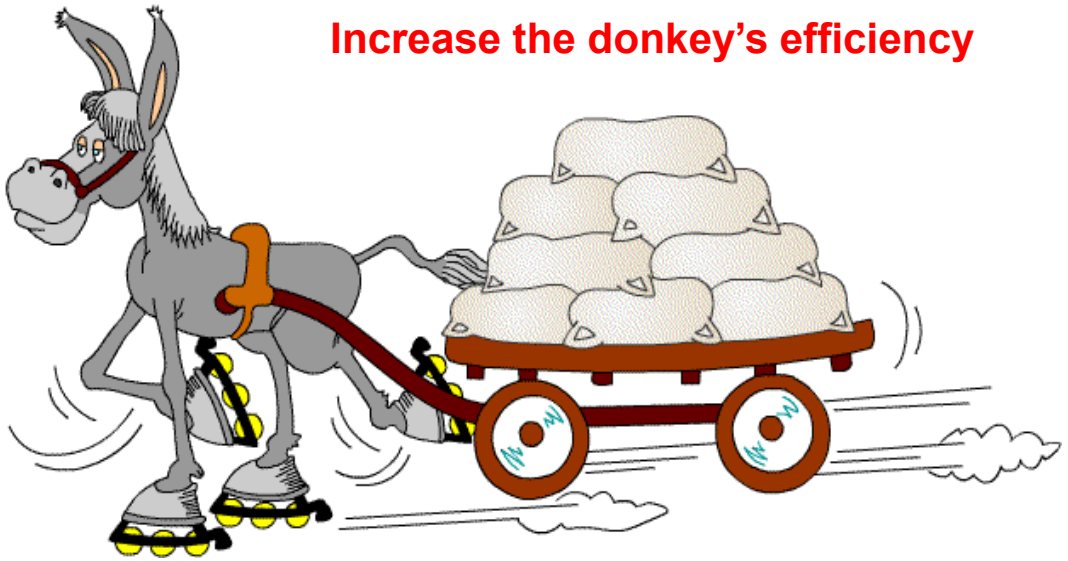
Vasodilators: Hydralazine/isosorbide dinitrate

- **Dosing and administration considerations**
- **(a) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) starting at 1 tablet three times daily with a goal dose of 2 tablets three times daily**
- **(b) Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses**
- **Monitoring**

✓**Headache**

✓**Hypotension**

✓**Drug-induced lupus (with hydralazine)**



Neprilysin Inhibitors (Sacubitril/valsartan)

- **Place in therapy**
- **In patients with chronic symptomatic NYHA class II or III HFrEF who cannot tolerate an ACE inhibitor or ARB, replacement by sacubitril/valsartan is recommended to further reduce morbidity and mortality (class I recommendation).**
- **Benefits**
- **Decreased composite endpoint of death from CV causes or hospitalization for HF**
- **Decreased all-cause mortality and CV death**
- **Decreased hospitalization for HF**

Sacubitril/valsartan

- **Mechanism of action**
- **Sacubitril—prodrug metabolized to an active metabolite that inhibits neprilysin, increasing levels of natriuretic peptides, the NPs are considered to be a favorable form of neurohormonal activation. Among their positive attributes are antagonism of the renin–angiotensin system, inhibition of sympathetic outflow, and Endothelin-1 (ET-1) antagonism. The net effect is peripheral and coronary vasodilation decreasing preload and afterload.**
- **Valsartan—ARB, selectively blocks the angiotensin I receptor and inhibits angiotensin II–dependent aldosterone release**
- **Dosing and administration considerations**
- **Initial dose: Not currently taking ACE inhibitor or ARB, switching from low dose ACE inhibitor or ARB, or eGFR <30 mL/min/m2: sacubitril 24 mg/ valsartan 26 mg twice daily**
- **Switching from a standard dose ACE inhibitor or ARB: sacubatril 49 mg/valsartan 51 mg twice daily**
- **Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/ valsartan 103 mg twice daily, as tolerated.**
- **If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.**
- **Because sacubitril is a neprilysin inhibitor, BNP will increase with use. However, NT-proBNP levels will not change.**

Ivabradine

❑ **Place in therapy**

✓ **Ivabradine can be beneficial to reduce HF hospitalizations for patients with symptomatic (NYHA class II and III), stable, chronic HFrEF (LVEF of 35% or less) who are receiving evidence-based therapies, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm (SR) with an HR of 70 beats/minute or greater at rest NOT fully managed by β-blockers (class IIa recommendation).**

❑ **Benefits**

✓ **Decreased composite endpoint of CV death or hospitalization for HF**

✓ **Decreased hospitalization for HF**

❑ **Mechanism of action: a novel heart rate lowering medicine selectively inhibits ('funny') channel (If) current leading to inhibition of the pacemaker current in the sinoatrial node, providing HR reduction**

Ivabradine

❑Dosing and administration considerations

- Given the well-proven mortality benefits of β-blocker therapy, patients should be receiving β-blockers at maximally tolerated or target doses or have a contraindication to β-blocker therapy before assessing the resting HR for consideration of ivabradine initiation.
- Initial dosing: 5 mg twice daily, After 2 weeks, adjust dose according to HR:
- Resting HR greater than 60 beats/minute: Increase dose by 2.5 mg twice daily.
- Resting HR 50–60 beats/minute: Continue current dose.
- Resting HR less than 50 beats/minute or signs/symptoms of bradycardia: Decrease dose by 2.5 mg twice daily.
- Maximum dose: 7.5 mg twice daily
- Contraindications: Acute decompensated heart failure (ADHF), BP <90/50 mm Hg, resting HR <60 beats/min, sinoatrial block, concomitant use with strong CYP3A4 inhibitors (azole antifungals (such as ketoconazole), macrolide antibiotics)

❑ Monitoring

❑ Assess HR and rhythm for bradycardia and atrial fibrillation (AF) after 2 weeks of therapy initiation or modification and periodically thereafter

❑ Phosphenes: transient rings or spots of light in the visual field.

Other medication therapies

- **Anticoagulation** : Recommended for HF with permanent, persistent, or paroxysmal atrial fibrillation AF with an additional risk factor for stroke
- **Statins**: Not recommended solely on the basis of HF diagnosis
- **Antiarrhythmics**: Given the neutral effects on mortality, the preferred antiarrhythmics in patients with HFrEF are class III antiarrhythmic agent **dofetilide** (AF/atrial flutter) and **amiodarone**.
- **Nondihydropyridine (DHP) calcium channel blockers (CCBs)** with negative inotropic effects can be harmful in patients with a low EF and should be avoided (class III recommendation: harm).
- **DHP CCBs**: DHP CCBs have no proven benefit on morbidity or mortality in HF. Use of amlodipine can be considered for **HTN or ischemic heart disease** management in HF patients because of its neutral effects on morbidity and mortality.

Non-pharmacologic therapy

- **Prevent further cardiac injury.**

✓**Discontinue smoking.**

✓**Reduce weight if obese.**

✓ **Control HTN & DM.**

✓ **Decrease alcohol intake & Limit Na intake to 1.5- 2 g/day.**

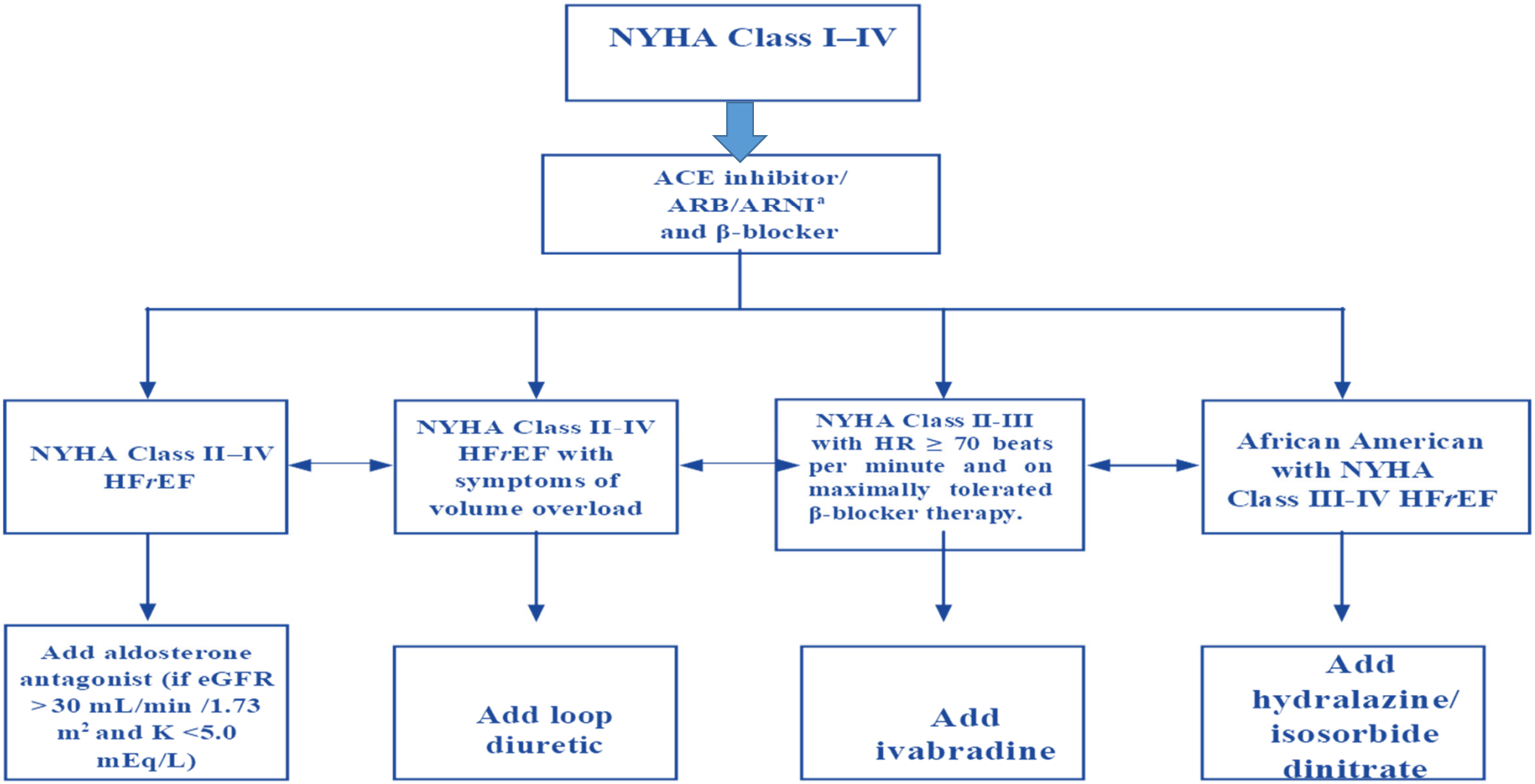
✓ **Treat sleep apnea.**

✓ **Educate patient about appropriate self-care.**

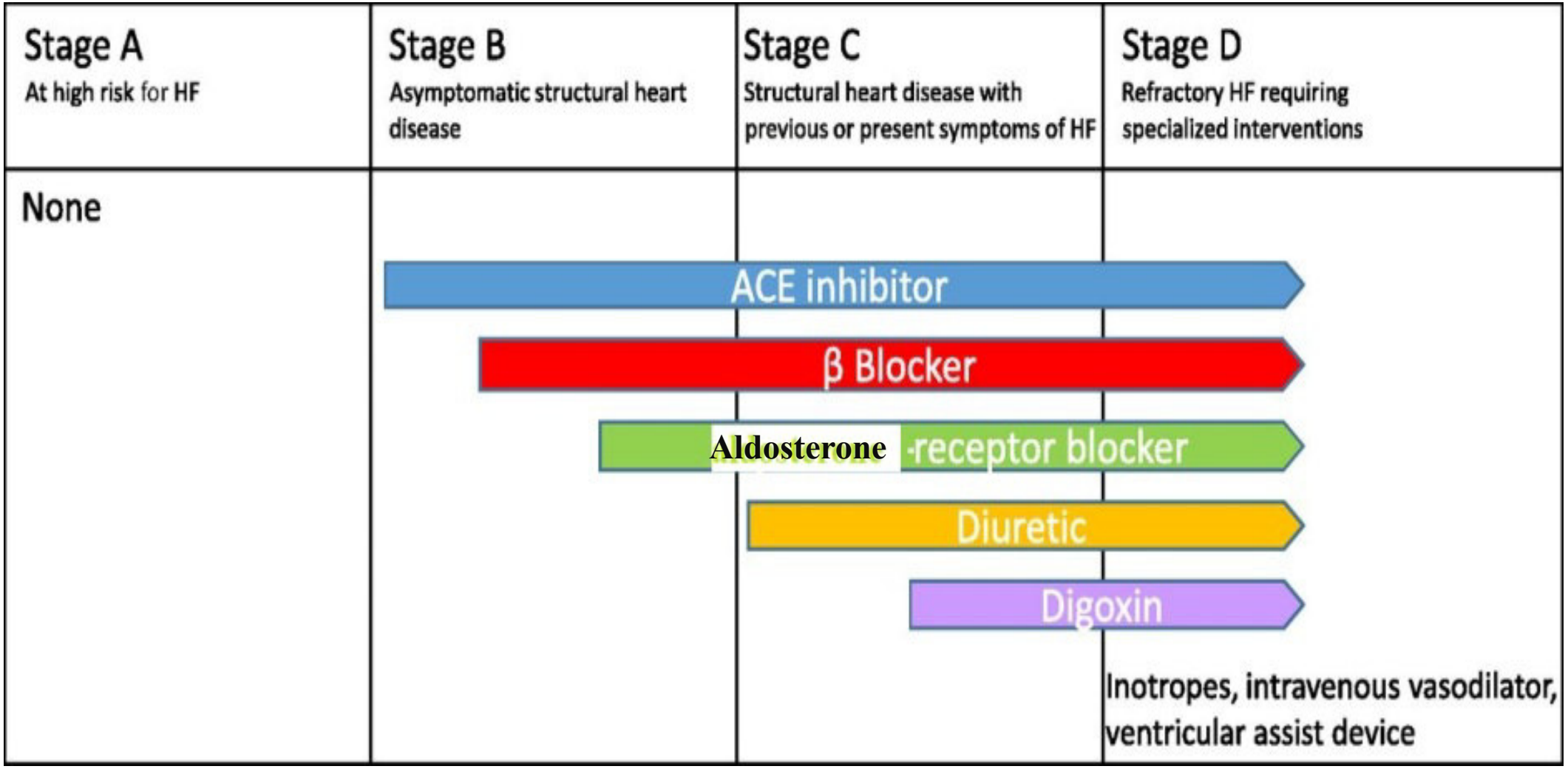
- **Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low.**
- **Modest exercise program benefits**
- **Influenza and pneumococcal vaccines**
- **COENZYME Q**
- **Monitor and appropriately replace electrolytes (to minimize risk of arrhythmias).**
- **Monitor for thyroid disease.**
- **Screen for and treat depression.**

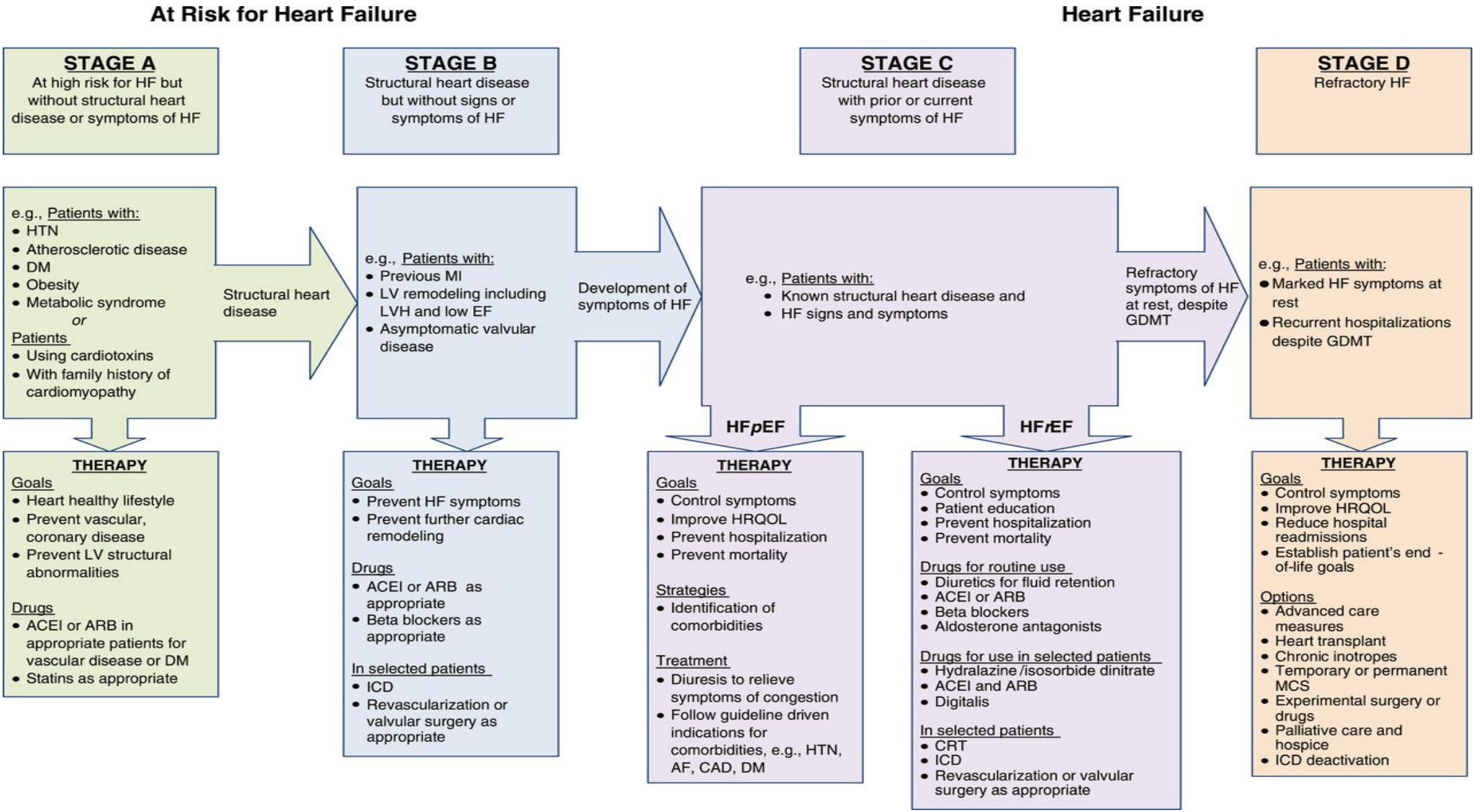
Device therapy

- Cardiac Resynchronization Therapy (CRT)
- Implanted Cardioverter Defibrillator (ICD)
- Angioplasty
- Left ventricle device assist
- Heart transplantation



Algorithm for pharmacologic management of heart failure with reduced ejection fraction.


Stage A
At high risk for HF
Stage B
Asymptomatic structural heart disease
Stage C
Structural heart disease with previous or present symptoms of HF
Stage D
Refractory HF requiring specialized interventions
None
ACE inhibitor
β Blocker
Aldosterone -receptor blocker
Diuretic
Digoxin
Inotropes, intravenous vasodilator, ventricular assist device


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
e.g., Patients with:
• HTN
• Atherosclerotic disease
• DM
• Obesity
• Metabolic syndrome
or
Patients
• Using cardiotoxins
• With family history of cardiomyopathy
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
• HF signs and symptoms
Refractory symptoms of HF at rest, despite GDMT
e.g., Patients with:
• Marked HF symptoms at rest
• Recurrent hospitalizations despite GDMT
HFpEF
HFrEF
THERAPY
Goals
• Heart healthy lifestyle
• Prevent vascular, coronary disease
• Prevent LV structural abnormalities
Drugs
• ACEI or ARB in appropriate patients for vascular disease or DM
• Statins as appropriate
THERAPY
Goals
• Prevent HF symptoms
• Prevent further cardiac remodeling
Drugs
• ACEI or ARB as appropriate
• Beta blockers as appropriate
In selected patients
• ICD
• Revascularization or valvular surgery as appropriate
THERAPY
Goals
• Control symptoms
• Improve HRQOL
• Prevent hospitalization
• Prevent mortality
Strategies
• Identification of comorbidities
Treatment
• Diuresis to relieve symptoms of congestion
• Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
THERAPY
Goals
• Control symptoms
• Patient education
• Prevent hospitalization
• Prevent mortality
Drugs for routine use
• Diuretics for fluid retention
• ACEI or ARB
• Beta blockers
• Aldosterone antagonists
Drugs for use in selected patients
• Hydralazine /isosorbide dinitrate
• ACEI and ARB
• Digitalis
In selected patients
• CRT
• ICD
• Revascularization or valvular surgery as appropriate
THERAPY
Goals
• Control symptoms
• Improve HRQOL
• Reduce hospital readmissions
• Establish patient's end - of-life goals
Options
• Advanced care measures
• Heart transplant
• Chronic inotropes
• Temporary or permanent MCS
• Experimental surgery or drugs
• Palliative care and hospice
• ICD deactivation

HFpEF or Diastolic dysfunction

- **1. Class I recommendations**
- **a. HTN should be well controlled & Diuretics should be used for symptom relief in volume overload.**
- **2. Class IIa recommendations**
- **a. Coronary revascularization is reasonable in patients with CHD.**
- **b. Management of AF is reasonable to improve symptomatic HF.**
- **c. The use of β-blockers, ACE inhibitors, and ARBs in patients with HTN is reasonable to control BP.**
- **3. Class IIb recommendation: Use of ARAs might be considered to decrease hospitalizations in patients with HFrEF already on ACE inhibitors/ARBs and β-blockers.**
- **4. Other recommendations**
- **a. Control tachycardia.**

✓ **Tachycardia decreases the time for the ventricles and coronary arteries to fill with blood.**

✓ **Control of HR improves symptoms of HF.**

✓ **Can use β-blockers or non-DHP CCBs**

- **b. Symptoms of breathlessness can be relieved using nitrates in addition to diuretics.**

Acute decompensated heart failure (ADHF)

- **Acute decompensated heart failure (ADHF) is a sudden worsening of the signs and symptoms of heart failure, which typically includes difficulty breathing (dyspnea), leg or feet swelling, and fatigue.**
- **A.Precipitating Factors**
- **1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)**
- **2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, AF or other arrhythmias, concurrent infections, other acute CV disorders)**

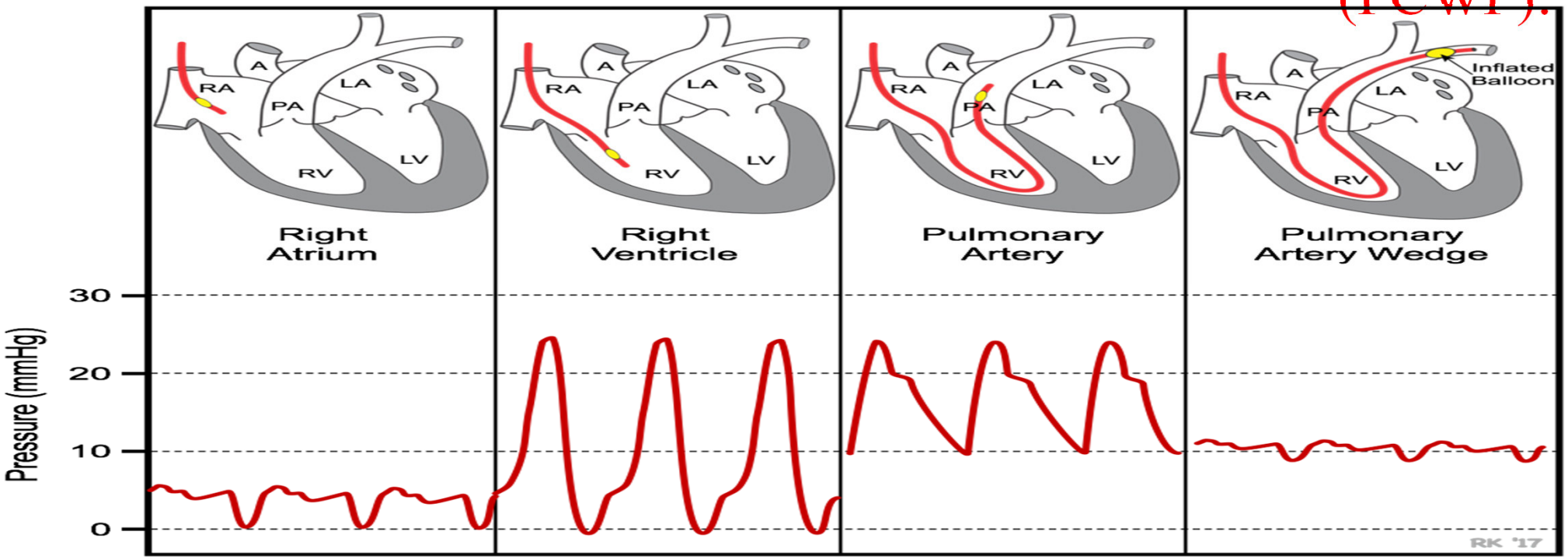
Acute decompensated heart failure

- **B. Diagnosis**
- **1. Must include a detailed history and physical examination**
- **2. B-type natriuretic peptide (BNP) or NT-proBNP is useful to support the diagnosis and establish the prognosis for acute decompensated heart failure (ADHF).**

✓ **High BNP concentrations (greater than 400 pg/mL) are closely associated with acute HF.**

- **3. Hemodynamic monitoring**
- **a. Hemodynamic monitoring with pulmonary artery catheters helps in evaluating patients refractory to initial therapy, patients with unknown or unclear volume status, and patients with clinical significant hypotension or worsening renal function.**

Pulmonary capillary wedge pressure الضغط الإسفيني الشعيري الرئوي (PCWP):



Pulmonary capillary wedge pressure (PCWP): provides an indirect estimate of left atrial pressure (LAP). PCWP is measured by inserting balloon-tipped, multi-lumen catheter (Swan-Ganz catheter) into a peripheral vein (e.g., jugular or femoral vein), then advancing the catheter into the right atrium, right ventricle, pulmonary artery, and then into a branch of the pulmonary artery.

Hemodynamic Values in Patients with ADHF and Sepsis

- **CO = stroke volume × HR. (L/min)**
- **Cardiac index (CI) = CO/body surface area. (L/min/m^2). Cardiac index (CI) indicates the degree of perfusion.**
- **Pulmonary capillary wedge pressure (PCWP): indicates fluid status.**

✓ **It is helpful to measure PCWP to diagnose the severity of left ventricular failure and to quantify the degree of mitral valve stenosis.**

✓ **15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.**

- **MAP = diastolic blood pressure (DBP) + [⅓(SBP − DBP)]. Or = (SBP + 2 (DBP))/3**
- **Systemic vascular resistance (SVR; dynes/s/cm5) (Left ventricular afterload)**

(SVR = [(MAP − CVP)/CO] × 80. **CVD: Central venous pressure: normal** 2–6 mm Hg

- **BP = CO × SVR.**

Hemodynamic Values in Patients with ADHF and Sepsis

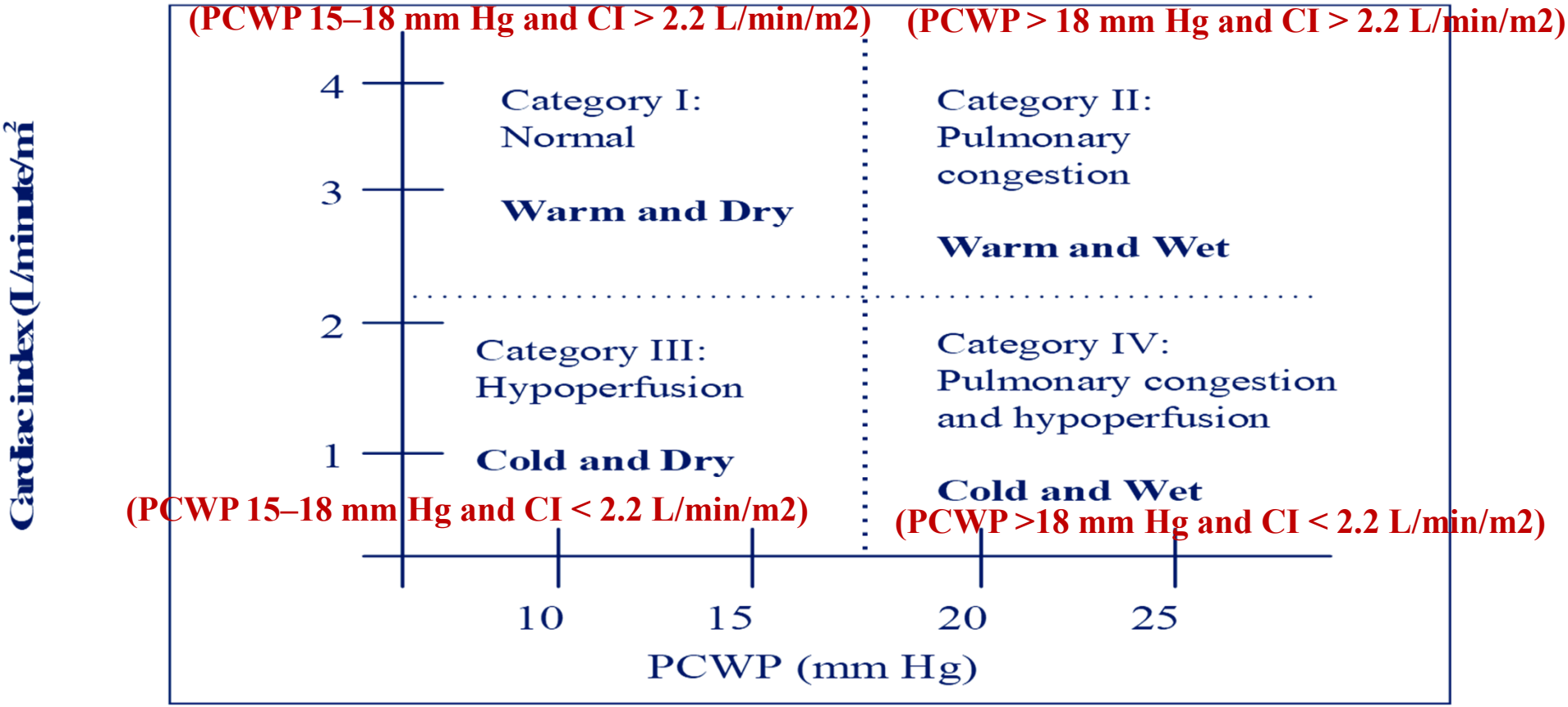
Parameter	Normal Value	Typical ADHF Value	Typical Sepsis Value
Mean arterial pressure (MAP; mm Hg)	80–100	60–80	60–80
Heart rate (HR; beats/min)	60–80	70–90	90–100
Cardiac output (CO; L/min)	4–7	2–4	5–8
Cardiac index (CI; L/min/m2)	2.8–3.6	1.3–2	3.5–4
Pulmonary capillary wedge pressure (mm Hg) PCWP	8–12	18–30	5–8
Systemic vascular resistance (SVR; dynes/s/cm5)	900–1400	1500–3000	300–800
Central venous pressure (CVP; mm Hg)	2–6	6–15	2–6

Acute decompensated heart failure

- **C. Clinical Presentation**
- **1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function.**
- **2. “Wet or dry” is commonly used to describe volume status.**
- **3. “Warm or cold” is used to describe cardiac function or ability to perfuse tissues.**

Acute decompensated heart failure

- **C. Clinical Presentation**



Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in acute decompensated heart failure. PCWP = pulmonary capillary wedge pressure.

General ADHF Management Based on Hemodynamic Subset

Subset and Description	Treatment
Subset I: Warm and Dry (normal parameters) (PCWP 15–18 mm Hg and CI > 2.2 L/min/m2)	- Optimize oral medications
Subset II: Warm and Wet (pulmonary or peripheral congestion) (PCWP > 18 mm Hg and CI > 2.2 L/min/m2)	- IV diuretics ± IV vasodilators (venous) - If symptoms persist, adjunctive strategies to overcome diuretic resistance may be necessary
Subset III: Cold and Dry (hypoperfusion ± orthostasis) (PCWP 15–18 mm Hg and CI < 2.2 L/min/m2)	- If PCWP < 15 mm Hg, IV Fluids until PCWP = 15–18 mm Hg - If PCWP ≥ 15 mm Hg, SBP < 90 mm Hg, IV inotrope - If PCWP ≥ 15 mm Hg, SBP ≥ 90 mm Hg, IV vasodilator (arterial) ± IV vasopressor, if needed
Subset IV: Cold and Wet (pulmonary/peripheral congestion + hypoperfusion) (PCWP >18 mm Hg and CI < 2.2 L/min/m2)	- IV diuretics + - If SBP ≥ 90 mm Hg, IV vasodilator (arterial) - If SBP < 90 mm Hg, IV inotrope ± IV vasopressor, if needed

Important Notes

- **Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.**
- **Venous vasodilator: Reduces PCWP.**
- **Adjunctive strategies for overcoming diuretic resistance include increasing the loop diuretic dose; changing to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and, in select patients, using ultrafiltration OR vasopressin antagonist.**
- **Arterial vasodilator: Reduce systemic vascular resistance with compensatory increase in CI.**
- **Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.**
- **IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF.**
- **The major vasopressors include phenylephrine, norepinephrine, epinephrine, and vasopressin. Dopamine is a vasopressor with inotrope properties that is dose-dependent.**
- **Norepinephrine is recommended as the initial pressor for alpha and beta activation. Epinephrine may be added as a secondary pressor. Phenylephrine should be used with extreme caution because of the reflex bradycardia due to unopposed vagal action on the heart, which may be associated with its use**

Acute decompensated heart failure

- **Signs and Symptoms of ADHF**

Congestion (elevated PCWP)	Hypoperfusion (low CO)
Dyspnea on exertion or at rest	Fatigue
Orthopnea, paroxysmal nocturnal dyspnea	Altered mental status or sleepiness
Peripheral edema	Cold extremities
Rales	Worsening renal function
Early satiety, nausea, or vomiting	Narrow pulse pressure
Ascites	Hypotension
Hepatomegaly, splenomegaly	Hyponatremia
Jugular venous distension	
Hepatojugular reflux	

Chronic HF Therapy in the Setting of Acute Decompensation

- **1. It is recommended to continue guideline-directed medical therapies during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock).**
- **2. ACE inhibitors**

✓ **a. Caution with initiation or titration during aggressive diuresis**

✓ **b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.**

- **3. β-Blockers**

✓ **a. Do not discontinue in patients whose condition is stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).**

✓ **b. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.**

✓ **c. Should be initiated at a low dose only in stable, euvolemic patients**

✓ **d. Caution should be used when initiating in patients who have received inotropes during their hospital course.**

Chronic HF Therapy in the Setting of Acute Decompensation

- **4. Digoxin**

✓**a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.**

✓**b. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.**

✓**c. Caution if renal function begins to deteriorate or often fluctuates**

ADHF Therapy Overview

- 1. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
- 2. No therapy studied to date has been shown conclusively to decrease mortality.
- 3. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events and are guided by cardiac output (CO) and volume status.
- A. **Diuretics**: Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF

✓1. Considered first-line therapy for management of ADHF associated with fluid overload

✓2. No difference between bolus and continuous administration of intravenous diuretics

✓3. Administering high-dose intravenous diuretic (2.5 times the previous oral dose) is associated with greater fluid removal.

ADHF Therapy Overview

- **B. Vasodilator Therapy**
- **1. Used (with diuretics) primarily to manage pulmonary congestion or wet (subset II or IV) HF**
- **2. When adequate blood pressure is maintained, use in preference to inotropic therapy.**
- **3. Venodilators increase venous capacitance, resulting in lower preload to reduce myocardial stress.**
- **a. Nitroglycerin is commonly used as a venodilator.**
- **4. Vasodilators with arterial vasodilating properties (nitroprusside and nesiritide) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low CO.**
- **a. Sodium nitroprusside is usually reserved for patients:**

✓ **i. With invasive hemodynamic monitoring (i.e., pulmonary artery catheter)**

✓ **ii. Without end-organ dysfunction (i.e., cyanide and thiocyanate accumulation)**

✓ **iii. Only until hemodynamic stabilization is achieved**

- **b. Although nesiritide has potential benefit because of its unique mechanism of action (vasodilatory with natriuretic and diuretic effects), use is limited given its: Lack of efficacy in a large randomized trial, Longer half-life and greater risk of hypotension & High cost**
- **5. Vasodilators should be avoided in patients with symptomatic hypotension (i.e., SBP less than 90 mm Hg).**

	Sodium Nitroprusside (Nipride)	Nesiritide (Natrecor)	IV Nitroglycerin
Mechanism of action	Nitric oxide–induced stimulation of GC to convert GTP to cGMP	Recombinant B-type natriuretic peptide binds to natriuretic peptide receptor A to stimulate GC and production of cGMP; natriuretic mechanism unknown	Combines with sulfhydryl groups in vascular endothelium to create S-nitrosothiol compounds that mimic nitric oxide's stimulation of GC and production of cGMP
Clinical effects	Balanced arterial and venous vasodilator	Hemodynamic effects: ↓ PCWP and SVR, ↑ CI, minimal changes in HR Neurohormonal effects: ↓ NE, ET-1, and aldosterone Natriuretic effects at supratherapeutic doses	Preferential venous vasodilator > arterial vasodilator, arterial vasodilation at high doses
Indication	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF	Warm and wet ADHF, ACS, or hypertensive crises
Dosing	0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/ min every 10–20 min	2 mcg/kg IVB, 0.01 mcg/kg/min IV	5 mcg/min IV, increase by 5 mcg/min every 5–10 min up to 200 mcg/min
Typical dose	0.5–1 mcg/kg/min IV	0.01 mcg/kg/min IV; can omit bolus if low SBP	25–100 mcg/min IV, titrated to response
Half-life	< 10 min	18 min	1–3 min
Elimination	Cyanide hepatically metabolized, thiocyanate renally excreted	Natriuretic peptide receptor C (no renal or hepatic adjustment)	Inactive metabolites in urine
AEs	Hypotension or cyanide or thiocyanate toxicity	Primarily hypotension (up to 1 hr), tachycardia (less than inotropes)	Hypotension, reflex tachycardia, headache, tachyphylaxis

ADHF Therapy Overview

- C. Inotropic Therapy
- 1. Used primarily to manage hypoperfusion or cold (subset III or IV) HF
- a. Useful for symptom relief in patients with a low SBP (less than 90 mm Hg) or symptomatic hypotension
- b. Useful in patients with end-organ dysfunction (i.e., acute kidney injury, altered mental status, systemic hypoperfusion, hypotension, or CV collapse)
- c. Useful in patients whose disease is refractory to other HF therapies
- d. Useful as a bridge to an LV assist device or to a heart transplant or as palliative care
- 2. It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure [PCWP] 15–18 mm Hg) before administering inotropic therapy.
- 3. Given the risk of sequelae, it is reasonable to consider vasodilators before inotropes.
- a. Both milrinone and dobutamine are proarrhythmic.
- b. Inotropes increase mortality compared with vasodilator therapy.
- 4. Monitor continuously for arrhythmias.

ADHF Therapy Overview

- **C. Inotropic Therapy**
- **5. Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages, but the choice of inotropic therapy is very individualized.**
- **a. Milrinone may be favored:**

✓**i. To avoid tapering or discontinuing home β-blocker**

✓**ii. When pulmonary artery pressures are high**

- **b. Dobutamine may be favored in:**

✓**i. Severe hypotension**

✓**ii. Bradycardia**

✓**iii. Thrombocytopenia**

✓**iv. Severe renal impairment (Renal Shut Down)**

ADHF Therapy Overview

	Dobutamine (Dobutrex)	Milrinone (Primacor)
Mechanism of action	β1-Agonist: Stimulates AC to convert ATP to cAMP to ↑ CO; slight peripheral vasodilation	PDE inhibitor: Inhibits cAMP breakdown in heart to ↑ CO and in vascular smooth muscle to ↓ SVR
Clinical effects	Positive inotropic, chronotropic, lusitropic effects	Positive inotropic and lusitropic effects, no direct chronotropic effects
Indication	ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP > 15 mm Hg)	
Dosing	Start 2.5–5 mcg/kg/min IV; may titrate to max of 20 mcg/kg/min	50 mcg/kg IVB (rarely administered), then 0.1–0.2 mcg/kg/min IV; may titrate to max of 0.75 mcg/kg/min
Typical dose	5 mcg/kg/min IV	No bolus, 0.1–0.375 mcg/kg/min IV
Half-life	2 min	1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min/1.73 m2
Elimination	Hepatically metabolized (inactive), renally eliminated	90% renal
AEs	Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use	Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use
Other comments	Consider in severe hypotension	Consider if receiving a β-blocker or in those with high pulmonary artery pressures

Dopamine

- Strong beta1-adrenergic, alpha-adrenergic, and dopaminergic effects are based on dosing rate
- Beta1 effects: 2-10 mcg/kg/min
- Alpha effects: >10 mcg/kg/min
- Dopaminergic effects: 0.5-2 mcg/kg/min
- 1-5 mcg/kg/min IV (low dose): May increase urine output and renal blood flow
- 5-15 mcg/kg/min IV (medium dose): May increase renal blood flow, cardiac output, heart rate, and cardiac contractitlity
- 20-50 mcg/kg/min IV (high dose): May increase blood pressure and stimulate vasoconstriction; may not have a beneficial effect in blood pressure; may increase risk of tachyarrhythmias

ADHF Therapy Overview

- **D. Vasopressin Antagonists**
- **1. Use is limited because of their significant cost and their limited effects on meaningful long-term ADHF outcomes.**
- **a. Should be viewed as "add on" therapy to aggressive diuresis and not as initial or adjunctive therapy for fluid removal**
- **b. Strict free water restriction is guideline recommended.**
- **c. Tolvaptan is FDA approved for clinically significant hyponatremia associated with HF.**
- **d. In those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L)**
- **e. In those with less marked hyponatremia (i.e., less than 135 mEq/L) having neurologic symptoms and who have no correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone)**


Thank
You!

Dyslipidemia: Updated Guidelines

ACC/AHA

National Lipid Association (NLA)

American Diabetes Association (ADA)

Dr. Mahmoud Samy, PhD.

Lecturer of Clinical Pharmacy

Overview

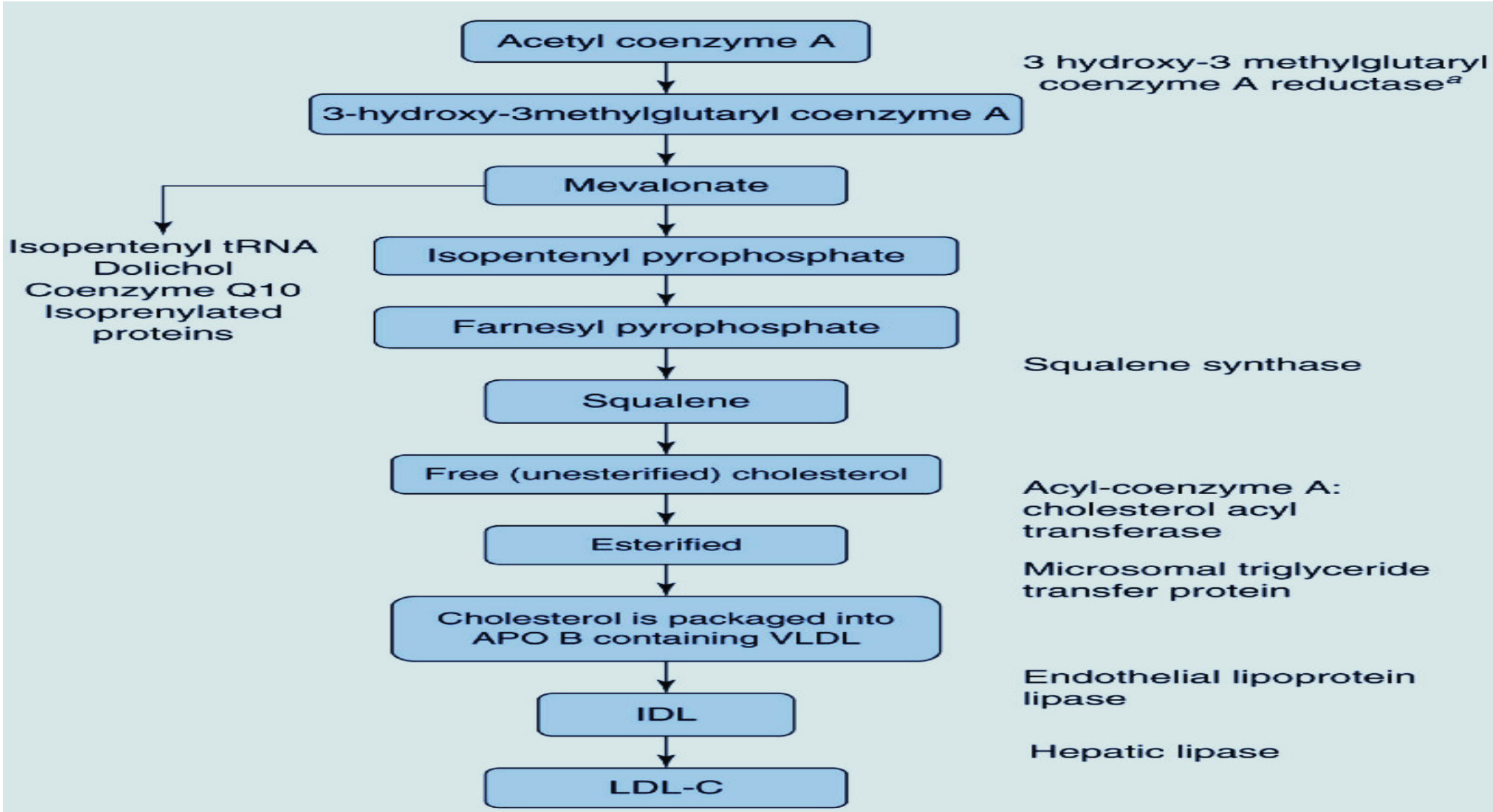
- **Dyslipidemias** (one or more abnormalities of blood lipids) play an important etiologic role in the pathogenesis of ASCVD, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease.
- Successful lifestyle changes and pharmacologic management of dyslipidemias have been shown to reduce the risk of ASCVD events such as heart attack and stroke.
- Cholesterol is a fatty substance manufactured in the liver and is carried throughout the body in the bloodstream.
- Cholesterol, an essential lipid, is the precursor molecule for the formation of bile acids, the synthesis of steroid hormones and the formation and integrity of cellular membranes.

Normal cholesterol metabolism

- Synthesis
  - Liver is key regulator of homeostasis
- Absorption
  - Largest source is biliary secretion, not diet.
  - Normal absorption: 50%
  - For cholesterol to be absorbed it must:
    - undergo hydrolysis (de-esterification by esterases)
    - be incorporated into micelles
    - be taken up by cholesterol transporter
    - be re-esterified and incorporated into chylomicrons

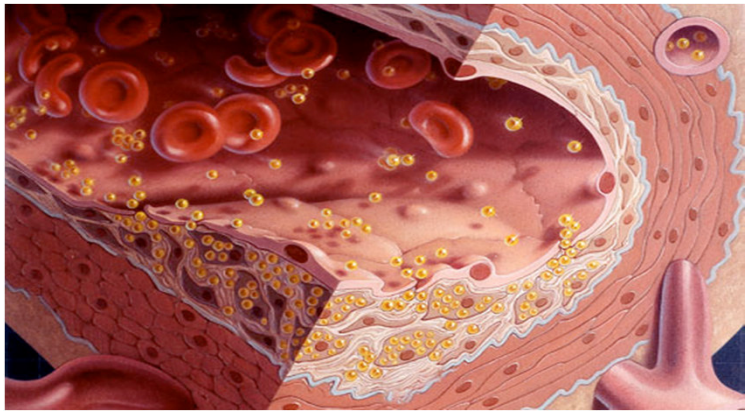
Cholesterol

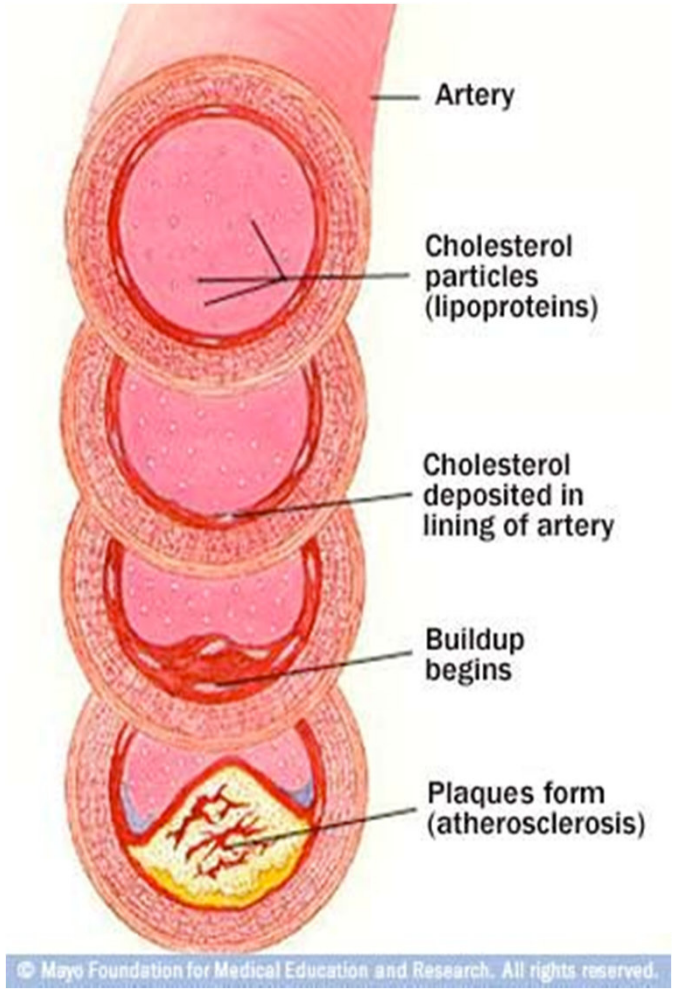
- High cholesterol is one of the major risk factors for coronary artery disease, heart attacks, and strokes. It also appears to boost the risk of Alzheimer's disease.
- The irreversible and rate-limiting step in cholesterol production is the conversion of β- hydroxyl-β-methylglutaryl coenzyme A (HMG-CoA) to mevalonic acid, which is catalyzed by **HMG-CoA reductase**.
- One of the most effective lipid-lowering therapies developed to date for managing dyslipidemias, HMG-CoA reductase inhibitors or statins, competitively interferes with the binding of substrate to this critical enzyme, thereby reducing the cellular synthesis of cholesterol.


Acetyl coenzyme A
3 hydroxy-3 methylglutaryl coenzyme A reductase[a]
3-hydroxy-3methylglutaryl coenzyme A
Mevalonate
Isopentenyl tRNA
Dolichol
Coenzyme Q10
Isoprenylated proteins
Isopentenyl pyrophosphate
Farnesyl pyrophosphate
Squalene synthase
Squalene
Free (unesterified) cholesterol
Acyl-coenzyme A: cholesterol acyl transferase
Esterified
Microsomal triglyceride transfer protein
Cholesterol is packaged into APO B containing VLDL
Endothelial lipoprotein lipase
IDL
Hepatic lipase
LDL-C

Symptoms

- High cholesterol does not cause any symptoms.
- Too much cholesterol may lead to a buildup of plaque inside the arteries.
- This is known as atherosclerosis, a condition that causes narrowing of the space available for blood flow
- This is known as atherosclerosis, a condition that causes narrowing of the space available for blood flow.





Lipoproteins

- Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation.
- Lipoproteins consist of esterified and unesterified cholesterol, TGs, and phospholipids and protein components named apolipoproteins that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors.
- The five most clinically relevant apolipoproteins are B-100, C, E, A-I, and A-II.
- There are six major lipoproteins in blood: chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL); lipoprotein a (Lp(a), and High-density lipoprotein (HDL).

Lipoproteins

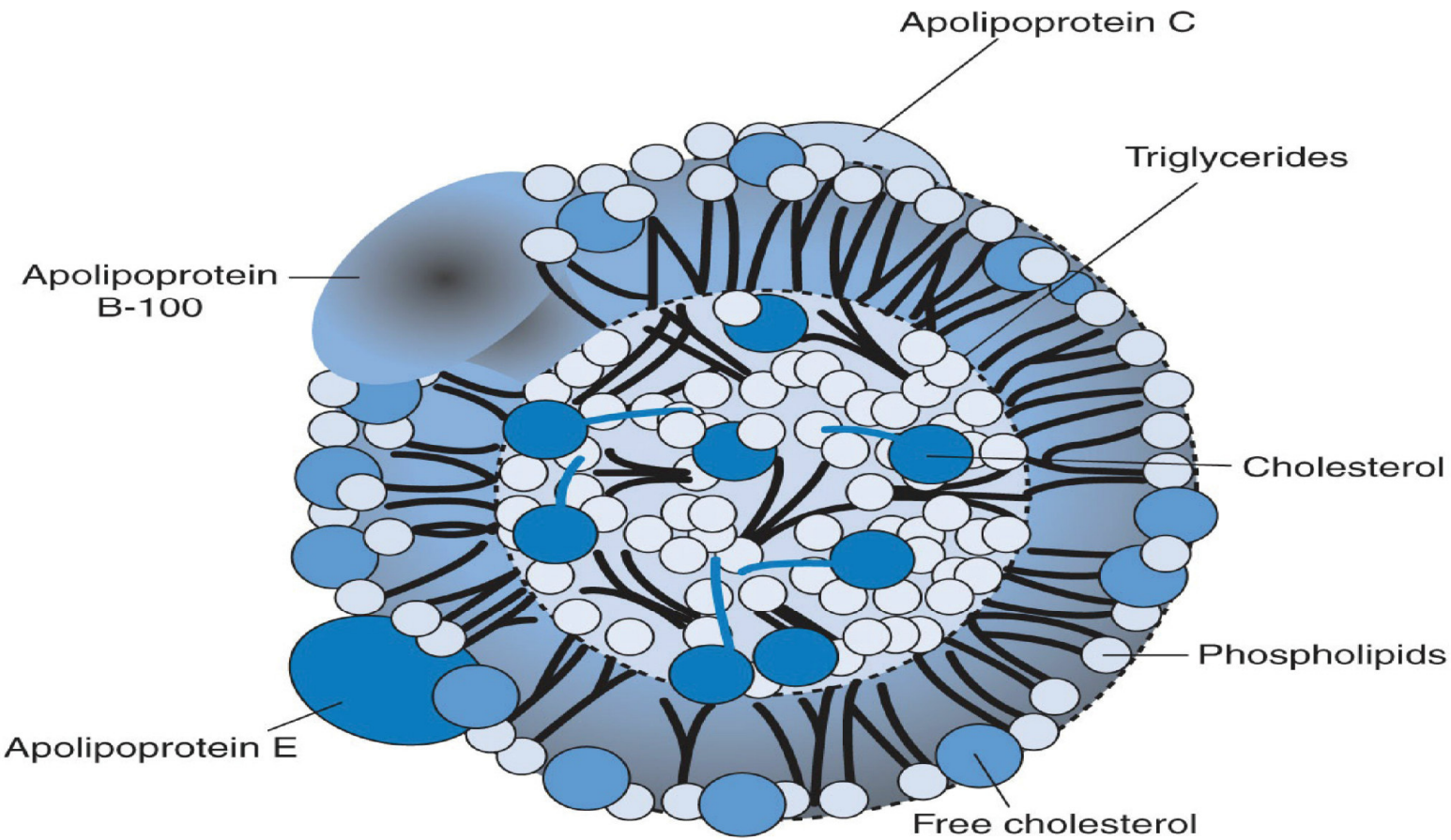


Figure 8-3 Basic structure of lipoproteins. Lipoproteins vary in the amount of cholesterol esters and triglyceride content. Additionally, they have varying numbers and types of surface apolipoproteins.

VLDL

- VLDL particles normally contain 15% to 20% of the total blood cholesterol concentration and most of the total blood TG concentration. The concentration of cholesterol in these particles is approximately one-fifth of the total TG concentration; thus, if the total TG concentration is known, the VLDL-cholesterol (VLDL-C) level can be estimated by dividing total TGs by 5.
- Total cholesterol measures the combination of LDL, HDL, and VLDL in your bloodstream. VLDL is a precursor of LDL, the bad cholesterol.

LDL

- **LDL particles are cholesterol enriched and carry 60% to 70% of the total blood cholesterol. LDL plays a central role in the pathogenesis of atherosclerosis and is the primary target of lipid-lowering therapy. Approximately half of the LDL particles are removed from the systemic circulation by the liver; the other half may be taken up by peripheral cells or deposited in the intimal space of coronary, carotid, and other peripheral arteries, where atherosclerosis can develop.**
- **A total cholesterol score of under 180 or 200 mg/dL is considered healthy in most cases.**
- **LDL combines with other substances to clog the arteries.**
- **A diet high in saturated fats and trans fats tends to raise the level of LDL cholesterol.**

HDL

- Up to a third of blood cholesterol is carried by high-density lipoproteins or HDL or the good cholesterol.
- HDL particles transport cholesterol from peripheral, lipid-rich inflammatory cells in the arterial wall back to the liver, a process called reverse cholesterol transport
- HDL helps remove bad cholesterol, preventing it from building up inside the arteries.
- The higher the level of HDL cholesterol, the better. People with too little are more likely to develop heart disease.
- Cholesterol ester transfer protein (CETP) transfers cholesterol from HDL particles to VLDL and LDL in exchange for TGs, making the HDL particle less cholesterol rich. If the latter occurs, cholesterol may be returned to the liver for clearance from the circulation or delivered back to peripheral cells. Patients have been identified who have a deficiency of CETP and high plasma concentration of HDL-C which appears to be associated with a low incidence of CHD (Anacetrapib - CETP inhibitors)

Triglycerides

- The body converts excess calories, sugar, and alcohol into triglycerides, a type of fat that is carried in the blood and stored in fat cells throughout the body.
- People who are overweight, inactive, smokers, or heavy drinkers and those who eat a very high carbohydrate diet tend to have high triglycerides
- A triglycerides score of 150 or higher puts you at risk for metabolic syndrome, which is linked to heart disease and diabetes.
- Traditionally, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples have suggested that the difference is small for most lipid parameters. In most studies, non-fasting samples display a higher TG level of 0.3 mmol/L (27 mg/dL). This increment will be of no clinical significance.

Important Lab Values

- **Friedewald equation** **LDL-C: = TC –(HDL-C + VLDL-C)**

  LDL-C: = TC –(HDL-C + 0.2 TG)

- **HDL-C (High-density lipoprotein)**
- **Optimal: 60 mg/dL and above** **Borderline: 40 - 59 mg/Dl** **Risk of heart disease: Less than 40 mg/dL**
- **LDL-C (Low-density lipoprotein)**
- **Optimal: Less than 100 mg/dL** **Near optimal/above optimal: 100 - 129 mg/dL**
- **Borderline high: 130 - 159 mg/dL** **High: 160 - 189 mg/dL** **Very high: 190 mg/dL and above**

- **LDL HDL ratio** . LDL HDL ratio is one of the most popular measures of a heart disease risk.

  ideal: below 2.0 good: below 5.0 too high: above 5.0

- **Non-HDL-C = TC – HDL-C (Non-HDL cholesterol should be less than 130 (mg/dL)**
- The treatment goal for non-HDL-C is 30 mg/dL above the LDL-C treatment target. For example, if the LDL-C treatment goal is <70 mg/dL, the non-HDL-C treatment target would be <100 mg/dL
- **TC/HDL-C ratio** The goal is to keep the ratio below 5.0; the optimum ratio is 3.5. But even though this ratio can be a powerful predictor of heart disease risk, it is not used as a sole indicator for therapy.

Important Values

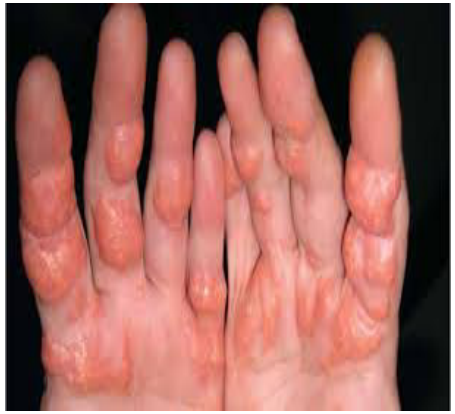
- **LDL-P (LDL particle number)** measures the actual number of LDL particles (particle concentration, nmol/L). It appears that LDL-P may be a stronger predictor of cardiovascular events than LDL-C. LDL-C is only a measure of the cholesterol mass within LDL-particles. Thus, LDL-C only indirectly reflects the atherogenic potential of LDL particles.
- LDL-P is measured by a so-called **NMR lipid profile test**.
- Ideal: <1000 Moderate: 1000-1299 Borderline High: 1300-1599
- High: >1600 Very High : > 2000
- **Apolipoprotein B (apoB)** and LDL-P, on the other hand, reflect the number of atherogenic particles, with no mention of cholesterol mass. Therefore apoB and LDL-P are believed to be better risk predictors than LDL-C.
- The normal range for apoB is 40-125 mg/dL.
- Usually less than 100 mg/dL is considered desirable in low or intermediate risk individuals.
- Less than 80 mg/dL is desirable in high risk individuals, such as those with cardiovascular disease or diabetes.

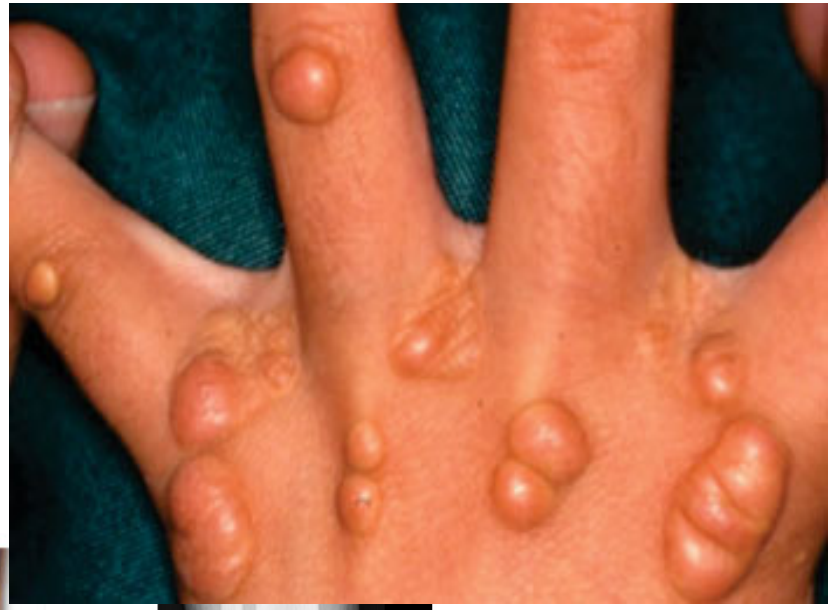
Common Cholesterol Disorders

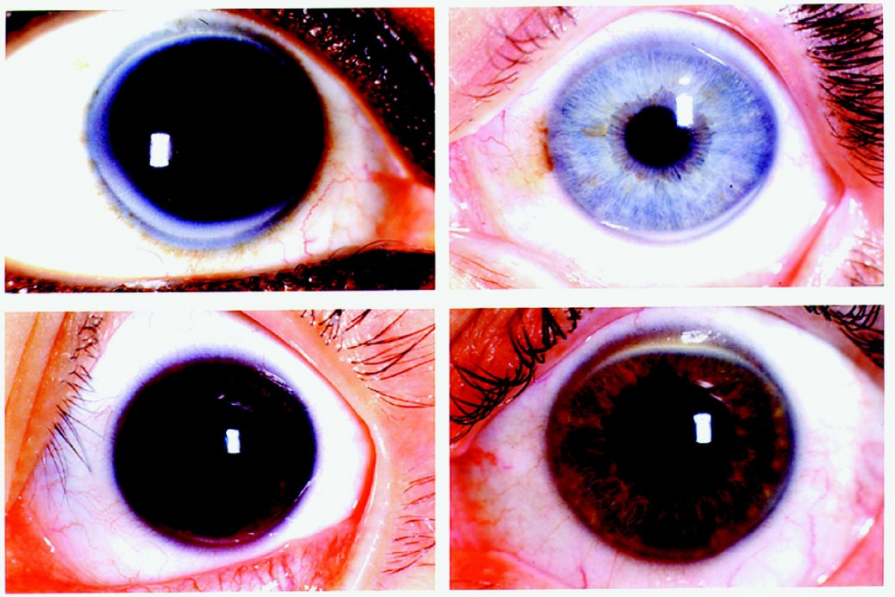
Lipoprotein Subclass Analysis (NMR)

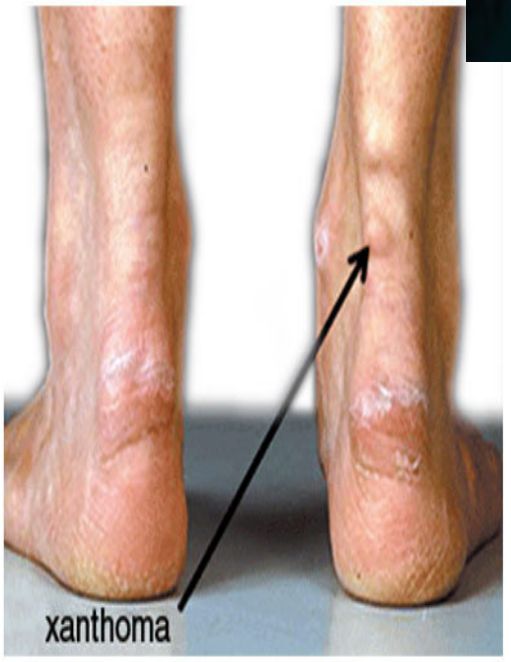
The Fredrickson classification, which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation.

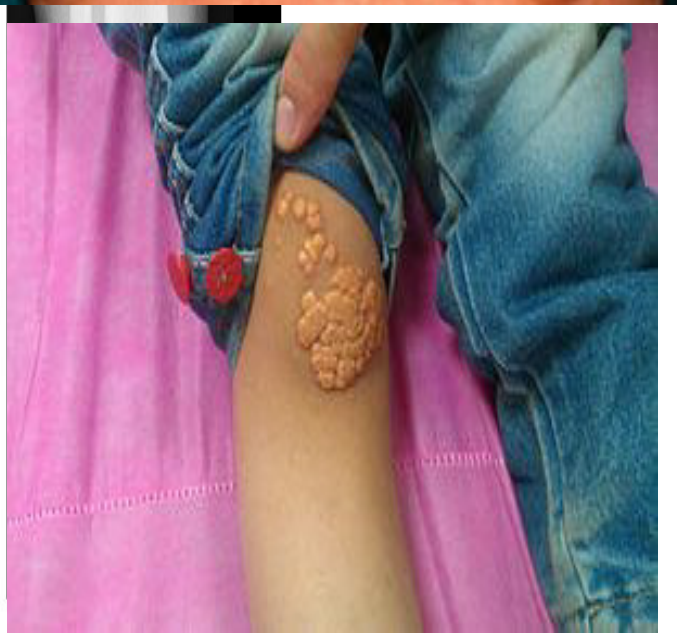
Disorder	Metabolic Defect	Lipid Effect	Main Lipid Parameter	Diagnostic Features
Polygenic Hypercholesterolemia	↓LDL clearance	↑LDL-C	LDL-C: 130–250 mg/dL	None distinctive
Atherogenic dyslipidemia	↑VLDL secretion ↑ApoC-III synthesis ↓LPL activity, ↓VLDL removal	↑TG, ↑Remnant VLDL ↓HDL ↑Small, dense LDL	TG: 150–500 mg/dL HDL-C: <40 mg/dL	Frequently accompanied by central obesity or diabetes
Familial hypercholesterolemia Heterozygous (HeFH)	Reduction in functional LDL receptor, defective apo B, gain of function mutations (Proprotein Convertase Subtilisin/Kexin Type 9) PCSK9	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus
Familial hypercholesterolemia Homozygous (HoFH)	Absent LDL receptors, defective apo B, gain-of function mutations PCSK9	↑LDL-C	LDL-C: >450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus; Affected individuals exhibit CHD by second decade of life. Aortic valvular disease (Systolic Murmur)
Familial defective apoB-100	Defective apoB on LDL and VLDL	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of CHD, tendon xanthomas
Dysbetalipoproteinemia (type III hyperlipidemia)	ApoE2/E2 phenotype, ↓VLDL remnant clearance	↑Remnant VLDL, ↑IDL	LDL-C: 300–600 mg/dL TGs: 400–800 mg/dL	Palmar xanthomas, tuberoeruptive xanthomas
Familial combined Hyperlipidemia	↑ApoB and VLDL Production	↑CH, TG, or both	LDL-C: 250–350 mg/dL TGs: 200–800 mg/dL	Family history, CHD Family history, Hyperlipidemia
Familial Hyperapobetalipoproteinema	↑ApoB production	↑ApoB	ApoB: >125 mg/dL	None distinctive
Hypoalphalipoproteinemia	↑HDL catabolism	↓HDL-C	HDL-C: <40 mg/dL	None distinctive

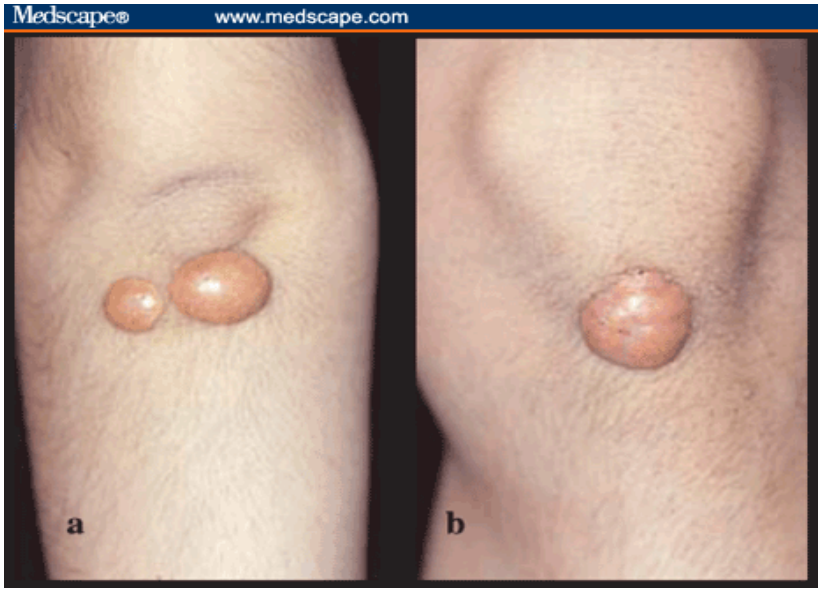







xanthoma

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The Fredrickson classification, which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation.

Type	Synonym	Defect	Serum abnormality	Clinical Features	Treatment	Serum appearance
Type 1	Familial Hyperchylomicronemia	Low LDL Altered ApoC2	Chylomicron ↑	Pancreatitis, Lipemia retinalis, skin eruptions, Xanthoma, Hepatosplenomegaly	Diet	Creamy top layer
Type IIa	Familial Hypercholestrolemia	↓LDL receptor	LDL↑	Xanthelasma, Arcus senilis, Tendon xanthomas	Cholestyramine or Cholestipol, Statins, Niacin	Clear
Type IIb	Familial Combined Hypercholestrolemia	↓LDL receptor & ↑Apo B	LDL & VLDL↑		Statins, Niacin, Fibrate	Clear
Type III	Familial dysbetalipoproteinemia	Apo E2 synthesis defect	IDL↑	Tubo-eruptive xanthomas, palmar xanthoma	Fibrate, Statins	Turbid
Type IV	Familial Hyperlipemia	↑VLDL production, ↓elimination	VLDL↑		Statins, Niacin, Fibrate	
Type V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Niacin, Fibrate	Creamy top layer & Turbid bottom

Ways to Lower Cholesterol

- Dietary Modifications
- Lifestyle Modifications
- Medications/Drugs
  - Statins
  - Non-Statins

Nonpharmacological recommendations

- 1. Lifestyle modification is cornerstone of initial intervention
- 2. Heart-healthy diet

✓ Recommend healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean Diet

✓ Emphasize consumption of fruits, vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes, and non-tropical vegetable oils

✓ Limit sweets, sugar-sweetened beverages, and red meats

✓ Lower intake of saturated fats and replace with unsaturated fats (especially polyunsaturated fats)

✓3. Regular exercise

- 4. Smoking cessation

Dietary Modifications

- Eat more fiber
- Know your fats
- Smart protein
- Low-carb diet

Know Your Fats

- **No more than 35% of your daily calories should come from fat.**
- **But not all fats are equal**
  - **Saturated Fats**
  - **Trans Fats**
  - **Unsaturated Fats**
- **Saturated fats -- from animal products and tropical oils -- raise LDL cholesterol.** Certain vegetable products have high **saturated fat** content, such as coconut oil and palm oil.
- **Trans fats increase bad cholesterol and lowers the good cholesterol**
- **These two bad fats are found in many baked goods, fried foods (doughnuts, french fries, chips), stick margarine, and cookies.**
- **Unsaturated fats may lower LDL when combined with other healthy diet changes. They're found in avocados, olive oil, and peanut oil.**

Smart Protein

- Meat and full-fat milk are protein but they are also major sources of cholesterol.
- Switch to soy protein, such as tofu.
- Fish is rich in omega-3 fatty acids, which can improve cholesterol levels.
- The AHA recommends eating fish at least twice a week.

Low-Carb Diet

- There's growing evidence that low-carb diets may be better than low-fat diets for improving cholesterol levels.
- In a two-year study funded by the National Institutes of Health, people who followed a low-carb plan had significantly better HDL (good cholesterol) levels than those who followed a low-fat plan.

Lifestyle Modifications

- Lose weight
  - Losing weight can help you reduce your levels of triglycerides, LDL, and total cholesterol.
  - Good cholesterol level tends to go up 1 point for every 6 pounds you lose.
- Quit smoking
  - When you stop smoking, your good cholesterol is likely to improve
- Exercise
  - Regular exercise also lowers bad cholesterol

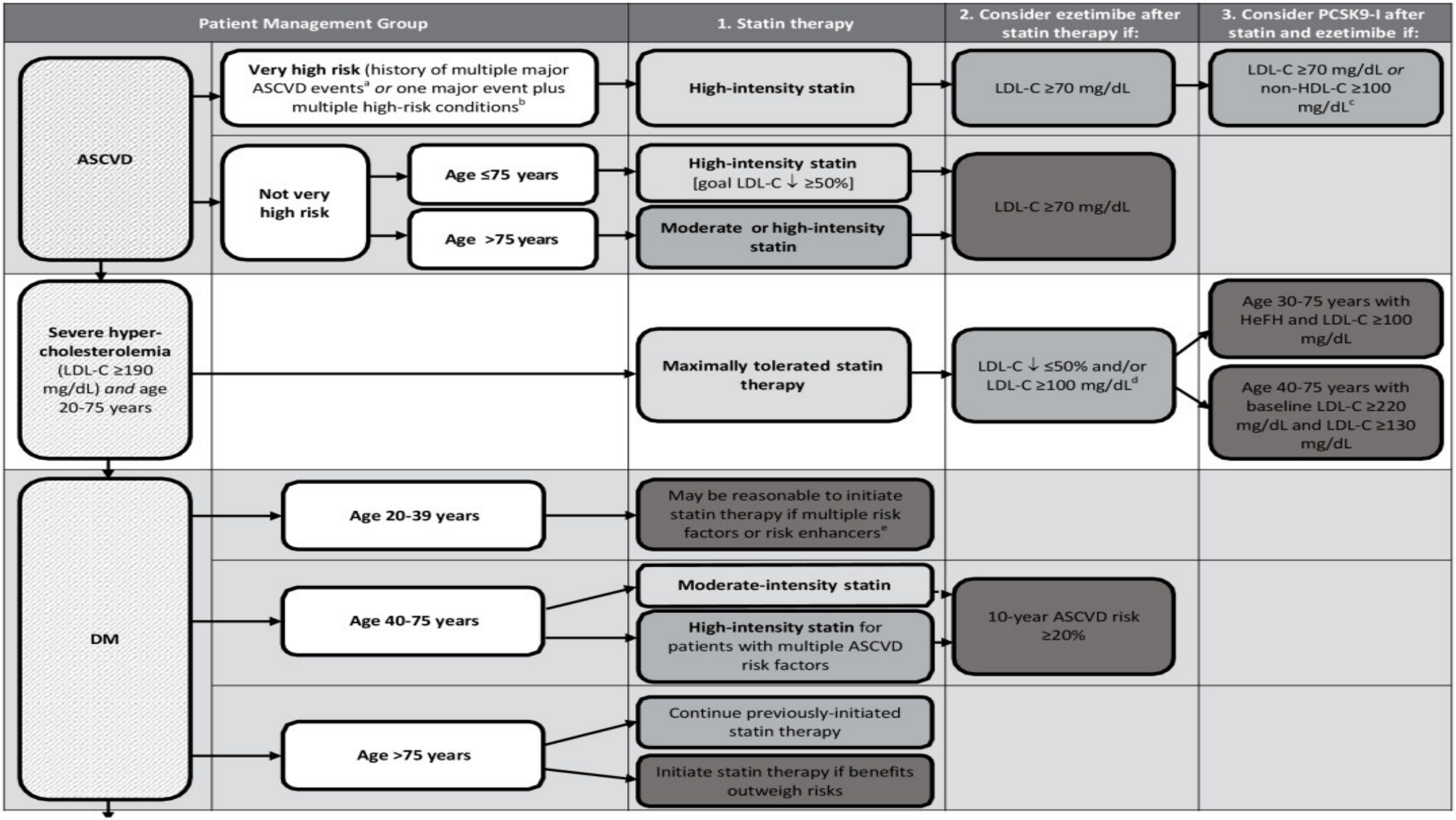
Pharmacologic recommendations

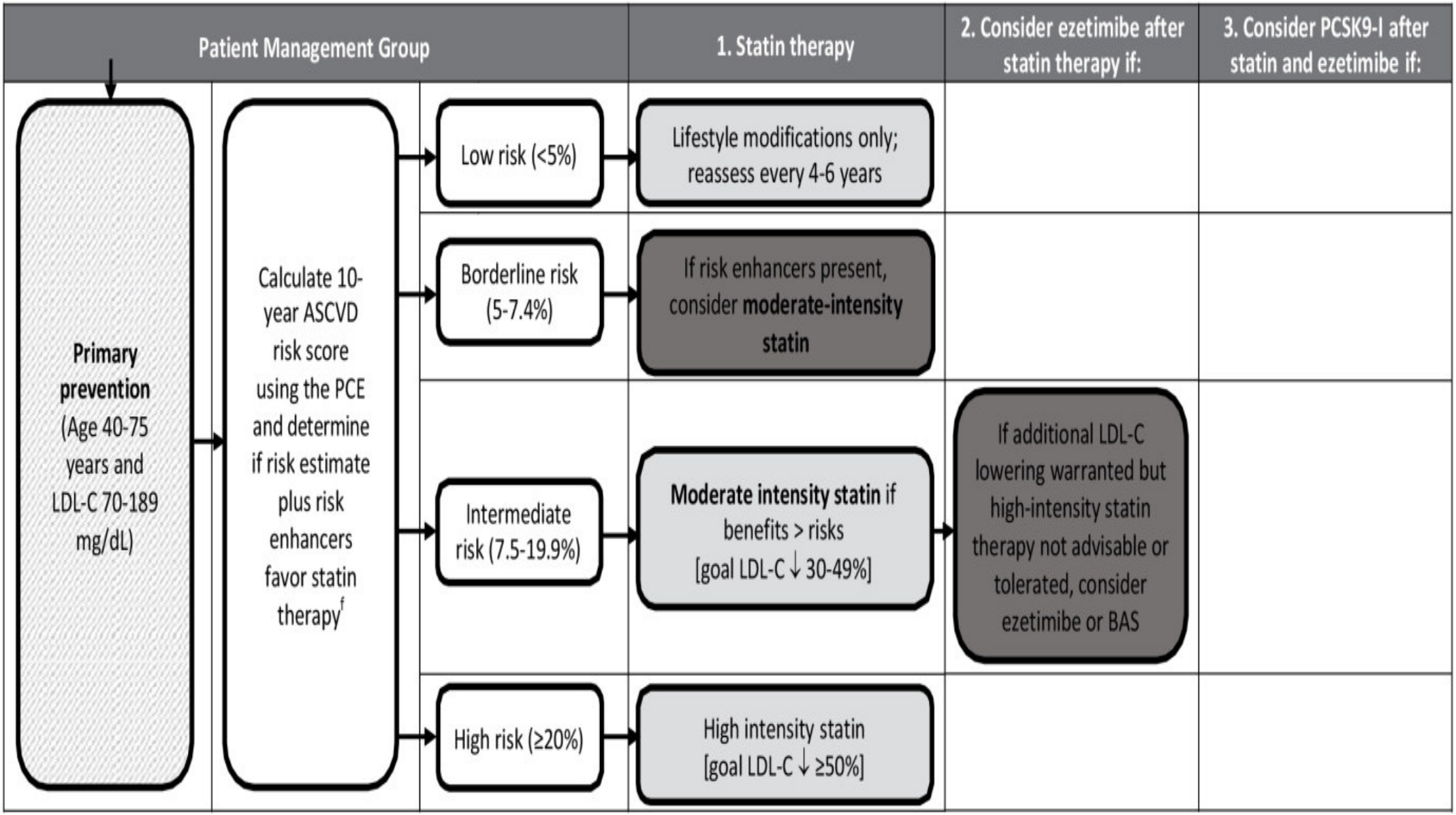
- **1. Therapy recommendations are divided into patient management groups:**
- **a. Secondary ASCVD prevention**
- **b. Severe hypercholesterolemia (LDL-C ≥190 mg/dL)**
- **c. Diabetes mellitus (DM)**
- **d. Primary prevention**
- **2. Pharmacologic management of dyslipidemia:**
- **a. First, initiate statin therapy if indicated. Optimize statin therapy (high intensity or maximally tolerated dose) before adding nonstatin therapy**
- **b. Second, add ezetimibe if indicated**
- **c. Third, consider Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I)**
- **3. Special populations**
- **a. Patients age >75 years**
- **i. Reasonable to initiate a moderate-intensity statin or continue a moderate- or high-intensity statin if benefits outweigh risks**
- **ii. Reasonable to discontinue statin therapy if patients have functional decline, multimorbidity, frailty, or reduced life expectancy limits potential benefits**

Common Secondary Causes of Elevated LDL-C and TG

Cause	Increase LDL-C	Increase TG
Medications	Amiodarone, cyclosporine, diuretics, glucocorticoids	Anabolic steroids, atypical antipsychotics, β-blockers, bile acid sequestrants, glucocorticoids, hormone therapy, protease inhibitors, raloxifine, retinoic acid, sirolimus, tamoxifen, thiazides
Dietary influences	Saturated or trans fats, weight gain, anorexia (higher levels of CETP)	Very low-fat diets, high carbohydrate intake (refined), excess alcohol, weight gain
Disease states and medical conditions	Nephrotic syndrome, biliary obstruction, hypothyroidism, obesity, pregnancy	Poorly controlled diabetes, hypothyroidism, obesity, pregnancy, nephrotic syndrome, chronic renal failure, lipodystrophies

Algorithm for statin and non-statin therapy recommendations based on patient management group


Patient Management Group
1. Statin therapy
2. Consider ezetimibe after statin therapy if:
3. Consider PCSK9-I after statin and ezetimibe if:
ASCVD
Very high risk (history of multiple major ASCVD events[a] or one major event plus multiple high-risk conditions[b]
High-intensity statin
LDL-C ≥70 mg/dL
LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL[c]
Not very high risk
Age ≤75 years
High-intensity statin [goal LDL-C ↓ ≥50%]
LDL-C ≥70 mg/dL
Age >75 years
Moderate or high-intensity statin
Severe hyper-cholesterolemia (LDL-C ≥190 mg/dL) and age 20-75 years
Maximally tolerated statin therapy
LDL-C ↓ ≤50% and/or LDL-C ≥100 mg/dL[d]
Age 30-75 years with HeFH and LDL-C ≥100 mg/dL
Age 40-75 years with baseline LDL-C ≥220 mg/dL and LDL-C ≥130 mg/dL
DM
Age 20-39 years
May be reasonable to initiate statin therapy if multiple risk factors or risk enhancers[e]
Age 40-75 years
Moderate-intensity statin
High-intensity statin for patients with multiple ASCVD risk factors
10-year ASCVD risk ≥20%
Age >75 years
Continue previously-initiated statin therapy
Initiate statin therapy if benefits outweigh risks


Patient Management Group
1. Statin therapy
2. Consider ezetimibe after statin therapy if:
3. Consider PCSK9-I after statin and ezetimibe if:
Primary prevention (Age 40-75 years and LDL-C 70-189 mg/dL)
Calculate 10-year ASCVD risk score using the PCE and determine if risk estimate plus risk enhancers favor statin therapy[f]
Low risk (<5%)
Lifestyle modifications only; reassess every 4-6 years
Borderline risk (5-7.4%)
If risk enhancers present, consider moderate-intensity statin
Intermediate risk (7.5-19.9%)
Moderate intensity statin if benefits > risks [goal LDL-C ↓ 30-49%]
If additional LDL-C lowering warranted but high-intensity statin therapy not advisable or tolerated, consider ezetimibe or BAS
High risk (≥20%)
High intensity statin [goal LDL-C ↓ ≥50%]

N.B

- **Major ASCVD events** are acute coronary syndrome (ACS) within the past 12 months, other history of myocardial infarction (MI), history of ischemic stroke, and symptomatic peripheral arterial disease
- **High risk conditions** are age ≥65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus (DM), hypertension, chronic kidney disease (eGFR 15-59 mL/min/1.73m2), current smoking, history of congestive heart failure, and persistently elevated LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe

N.B

- **Clinical evidence supports addition of PCSK9-I after maximally tolerated statin therapy, but adding ezetimibe first is more cost effective**
- **May consider adding a BAS to statin and ezetimibe if LDL-C reduction is <50% and fasting triglycerides ≤300 mg/dL, especially if ineligible for PCSK9-I therapy**
- **DM-specific risk enhancers include DM of long duration (≥ 10 years with type 2 DM or ≥ 20 years with type 1 DM); microvascular complications (albuminuria [≥ 30 mcg/mg creatinine], eGFR <60 mL/min/1.73m2, retinopathy, or neuropathy); or ankle-brachial index < 0.9**
- **If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium**

Risk assessment tools for primary prevention

- 1. Risk discussions and shared decision making with patients should consider whether lifestyle and ASCVD risk factors have been addressed, cost considerations, and a discussion of the potential benefits and adverse events of drug therapy (Cholesterol management plan).
- 2. Pooled Cohort Equation (PCE) to estimate 10-year ASCVD risk
- a. Measures hard ASCVD events: fatal and nonfatal MI and stroke
- b. Assists with identifying higher-risk patients for statin therapy
- c. Should not be used for patients with clinical ASCVD (stroke, transient ischemic attack (TIA), documented coronary artery disease (CAD) with stable angina, acute coronary syndromes (ACS), coronary or other arterial revascularization)
- d. Components of PCE: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
- i. Sex ii. Age iii. Race iv. TC v. HDL-C vi. SBP
- vii. Receiving treatment for high BP viii. DM ix. Smoker

Coronary artery calcium (CAC) score

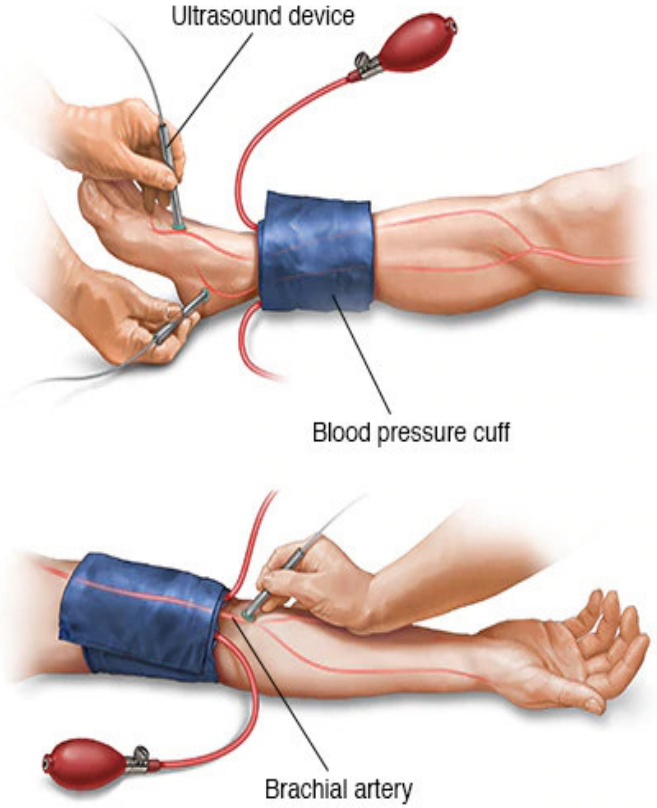
- Coronary artery calcium (CAC) score for additional risk-stratification. It measures the amount of calcium in the walls of the heart's arteries by computed tomography (CT)
- a. If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium
- b. Score = 0: consider no statin (unless DM, family history of premature coronary heart disease, or cigarette smoking present)
- c. Score = 1-99: favors statin if age ≥55
- d. Score ≥100: favors statin

Risk-enhancing factors

- a. Family history of premature ASCVD (males <55 years, females <65 years)
- b. Primary hypercholesterolemia (LDL-C 160-189 mg/dL or non-HDL-C 190-219 mg/dL)
- c. Metabolic syndrome
- d. Chronic kidney disease
- e. Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, HIV/AIDS
- f. History of premature menopause (age <40 years)
- g. History of preeclampsia
- h. High-risk race/ethnicity (e.g., South Asian ancestry)
- i. Elevated TG ≥175 mg/dL
- j. Elevated biomarkers such as high-sensitivity C-reactive protein, lipoprotein (a), apolipoprotein B
- k. Ankle-brachial index <0.9. The ankle-brachial index (ABI) is the ratio of the systolic blood pressure (SBP) measured at the ankle to that measured at the brachial artery.

Ankle-brachial index

- **k. Ankle-brachial index <0.9. The ankle-brachial index (ABI) is the ratio of the systolic blood pressure (SBP) measured at the ankle to that measured at the brachial artery.**
- **The ankle-brachial index test is a quick, noninvasive way to check for peripheral artery disease (PAD). The disease occurs when narrowed arteries reduce the blood flow to your limbs. PAD can cause leg pain when walking and increases the risk of heart attack and stroke.**
- **No blockage (1.0 to 1.4).**
- **Borderline blockage (0.91 to 0.99).**
- **PAD (less than 0.90).**



Metabolic Syndrome

- Clinical diagnosis requires more than 3 of the following risk factors:
  - Abdominal Obesity (waist circumference): men ≥ 102 cm (40 in) women ≥ 88 cm (35 in)
  - Elevated Triglycerides ≥ 150 mg/dL
  - Reduced HDL cholesterol: men < 40 mg/dL women < 50 mg/dL
  - Hypertension ≥ 130/85
  - Impaired fasting glucose ≥ 110 mg/dL

Hypertriglyceridemia

- **Risk Classification of Serum Triglycerides**
  - ✓ **Normal :<150 mg/dl** **Borderline high : 150–199 mg/dL**
  - ✓ **High :200–499 mg/dL** **Very high >500 mg/dL**
- **Primary goal is to prevent pancreatitis**
- **Evaluate for secondary causes**
- **Moderate hypertriglyceridemia (triglycerides [TG] 175-499 mg/dL)**
  - ✓ **Address and treat lifestyle factors, comorbidities, and medications which increase TGs**
  - ✓ **If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy**
- **Severe hypertriglyceridemia (TG ≥ 500 mg/dL)**
  - ✓ **If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy**
  - ✓ **Reasonable to initiate fibrate therapy to prevent acute pancreatitis, especially if fasting TG ≥ 1000 mg/dL**

Effect of Lipid-Lowering Medications on TG

Medication	% Decrease in TG
Statins	7–30
Fibrates	**20–50**
Niacin	**20–50**
Ezetimibe	5–11
Omega-3 fatty acids	**19–44**

Monitoring

- Measure fasting lipids 4-12 weeks after therapy initiation
- Measure fasting lipids every 3-12 months thereafter
- Periodically re-assess risk factors for ASCVD

Pharmacological Therapy

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)

- **1. General approach to initiating statin therapy:**
- **a. Lipid panel**
- **i. If LDL-C is higher than 190 mg/dL, evaluate for secondary causes. If primary, screen for familial hypercholesterolemia.**
- **ii. If TG 500 mg/dL or higher, treat hypertriglyceridemia**
- **b. Alanine aminotransferase (ALT):**
- **Evaluate patients with unexplained ALT more than 3x upper limit of normal**

✓ **Hemoglobin A1C**

✓ **Creatine kinase (if indicated)**

✓ **Evaluate for secondary causes or conditions that may affect statin safety**

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)

- **2. Efficacy**
- **a. When selecting a statin, consider its intensity.**
- **b. Reduce LDL-C by 24%–60%.**
- **c. Reduce TG by 7%–30%.**
- **d. Raise HDL-C by 5%–15%.**
- **e. Reduce major coronary events.**
- **f. Reduce CHD mortality.**
- **g.Reduce coronary procedures (percutaneous coronary intervention [PCI] or coronary artery bypass grafting).**
- **h. Reduce stroke.**
- **i. Reduce total mortality.**

Relative LDL-C-Lowering Efficacy of Statins

Atorva (mg)	Fluva (mg)	Pitava (mg)	Lova (mg)	Prava (mg)	Rosuva (mg)	Simva (mg)	%↓ LDL
—	20–40	1	20	10–20	—	10	30
10	80	2	40	40	—	20	38
20	—	4	80	80	5	40	41
40	—	—	—	—	10	—	47
80	—	—	—	—	20	—	55
—	—	—	—	—	40	—	63

Denotes low-intensity statin; lowers LDL-C by < 30%.

Denotes moderate-intensity statin; lowers LDL-C by 30% to < 50%.

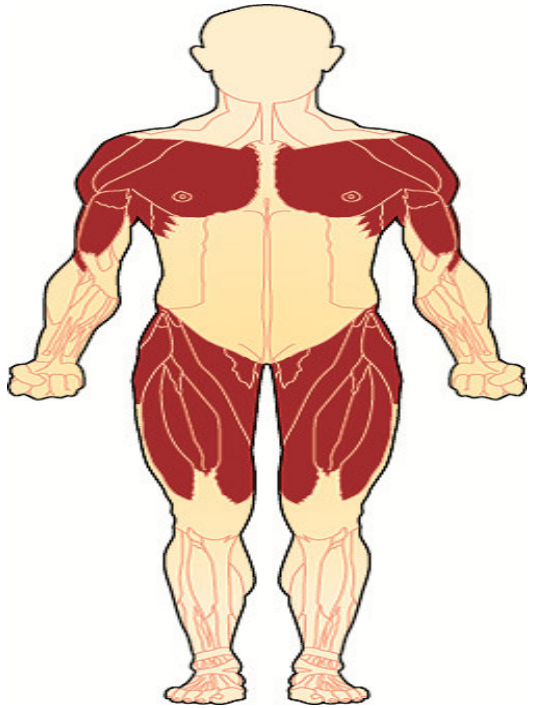
Denotes high-intensity statin; lowers LDL-C by ≥ 50%.

Statins

- **Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate- limiting step in production of cholesterol)**
- **Main adverse effects and monitoring**
- **a. Myopathy (can check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)**
- **b. Elevated liver enzymes**
- **i. Obtain LFTs at baseline in all patients**
- **ii. Perform repeated LFTs only when clinically indicated.**
- **iii. Monitor for symptoms of hepatic injury.**
- **Absolute contraindications**
- **a. Active liver disease, unexplained persistent elevations in hepatic transaminases**
- **b. Pregnancy**
- **c. Nursing mothers**
- **d. Certain medications**

Statins

- **Select drug interactions**
- **a. Fibrates: Increased risk of myopathy and rhabdomyolysis when coadministered with statins. Risk is greater with gemfibrozil than with fenofibrate.**
- **b. Niacin: Doses greater than 1 g/day increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.**
- **(Amiodarone, amlodipine , verapamil, diltiazem)**
- **Caution should be taken when administered with any drugs affecting their metabolism (clarithromycin, erythromycine, azoles antifungal)**
- **True statin-related myalgias are typically symmetric and are described as aching, soreness, stiffness, tenderness, weakness, or cramping of large proximal muscle groups.**



Differences exist between statins in regard to pharmacokinetics

	Bioavailability (%)	Half-life (hr)	Elimination/ Metabolism	Prodrug	Solubility
Atorvastatin	14	14	3A4	No	Lipophilic
Fluvastatin	24	3	2C9	No	Lipophilic
Lovastatin	< 5	2–3	3A4	Yes	Lipophilic
Pitavastatin	43-51	12	2C9	No	Lipophilic
Pravastatin	17	1.8	N/A	No	Hydrophilic
Simvastatin	< 5	2	3A4	Yes	Lipophilic
Rosuvastatin	20	19	2C9	No	Hydrophilic

Dosing of Statin Agents in CKD

Drug	Comments	Dose Recommended by KDIGO Guidelines
Atorvastatin	—	20 mg/day
Fluvastatin	Doses > 40 mg/day not studied in severe renal impairment	80 mg/day
Lovastatin	CrCl <30 mL/min: NTE 20 mg/day	Not studied
Pitavastatin	CrCl 15-59 mL/min: NTE 2 mg/day	2 mg/day
Pravastatin	CrCl <30 mL/min: Initial dose = 10 mg/day	40 mg/day
Simvastatinb	CrCl < 30 mL/min: Initial dose = 5 mg/day	40 mg/day (ezetimibe/simvastatin 10/20 mg/day)
Rosuvastatin	CrCl < 30 mL/min: NTE 10 mg/day	10 mg/day

Kidney Disease: Improving Global Outcomes (KDIGO) , NTE = not to exceed

Ezetimibe (cholesterol absorption Inhibitor)

- **1. Efficacy**
- **a. Lowers LDL-C by 18%–20%**
- **b. Can raise HDL-C by 1%–5%**
- **c. Lowers TG by 5%–10%**
- **2. Mechanism of action: Inhibition of cholesterol absorption**
- **3. Adverse effects and monitoring: Diarrhea, upper respiratory tract symptoms; no monitoring necessary**
- **4. Data suggest that combination with simvastatin is superior to simvastatin alone in prevention of CV events.**

PCSK9 Inhibitors

- 1. Efficacy: Lower LDL-C by an additional 45%–68% when combined with statin therapy; reduce CV events when added to statin therapy.
- 2. Mechanism of action: Monoclonal antibodies that inhibit a protein called PCSK9, increasing cholesterol clearance from the liver
- 3. Both Alirocumab & Evolocumab indicated for heterozygous familial hypercholesterolemia or clinical ASCVD; evolocumab also indicated for homozygous familial hypercholesterolemia (HoFH)
- 4. PCSK9 Inhibitors are only indicated for select patients already receiving maximally tolerated statin therapy and ezetimibe with either clinical ASCVD at very high risk or severe hypercholesterolemia.
- 5. Adverse effects: Injection-site reactions, respiratory infections
- 6. Dose:
- a. Evolocumab:
- i. Heterozygous familial hypercholesterolemia or clinical ASCVD: 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly
- ii. Homozygous familial hypercholesterolemia: 420 mg subcutaneously once monthly
- b. Alirocumab: Initial dose, 75 mg subcutaneously every 2 weeks or 300 mg subcutaneously every 4 weeks; if LDL-C reduction inadequate, can adjust dose to 150 mg subcutaneously every 2 weeks

Bile acid sequestrants (cholestyramine, colestipol, colesevelam)

- 1. Efficacy
- a. Reduce LDL-C by 15%–27%.
- b. Raise HDL-C by 3%–5%.
- c. May increase TG concentrations.
- d. Reduce major coronary events.
- e. Reduce CHD mortality.
- 2. Mechanism of action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.
- 3. Adverse effects: GI distress, constipation
- 4. Decreased absorption of many drugs including: warfarin, amiodarone, levothyroxine, ezetimibe, digoxin, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid sequestrant
- 5. Contraindications: Complete biliary obstruction, raised TG concentrations (especially greater than 400 mg/dL)

Niacin

- 1. Efficacy
- a. Lowers LDL-C by 5%–25%
- b. Lowers TG by 20%–50%
- c. Raises HDL-C by 15%–35%
- d. Reduces major coronary events
- e. Lowers lipoprotein (a)
- 2. Mechanism of action: Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces synthesis of TG, very-low-density lipoproteins, and LDL-C
- 3. Adverse effects and monitoring: Flushing, hyperglycemia, hyperuricemia, myopathy, upper GI distress, increased hepatic transaminases; monitor LFTs at baseline, every 6–12 weeks for first year and then yearly
- 4. Sustained release appears to be more hepatotoxic than extended-release or immediate-release preparations.
- 5. Extended-release niacin is less likely to cause flushing.
- 6. Contraindications: liver disease and active peptic ulcer disease. Caution in patients predisposed to gout
- 7. Flushing can be minimized by taking aspirin or an NSAID 30–60 minutes before niacin, taking at bed- time with food, using slow titration, and avoiding hot beverages, spicy foods, and hot showers around the time of administration.

Fibrates (Gemfibrozil, Fenofibrate and Clofibrate)

- **1. Efficacy**
- **a. Lower LDL-C by 5%–20% (with normal TG)**
- **b. May raise LDL-C with very high TG**
- **c. Lower TG by 20%–50%**
- **d. Raise HDL-C by 10%–20%**
- **2. Mechanism of action: Reduces rate of lipogenesis in the liver (Decrease VLDL)**
- **3. Adverse effects and monitoring: Dyspepsia, gallstones, myopathy, increased hepatic transaminases. Monitor LFTs every 3 months during first year and then periodically.**
- **4. Contraindications: Severe renal or hepatic disease, pre-existing gallbladder disease**
- **5. Indicated for treatment of severe hypertriglyceridemia, especially in patients with TG ≥ 1000 mg/dL.**

Omega-3 fatty acids

- 1. Contain varying ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
- a. Omega-3 acid ethyl esters: DHA and EPA
- b. Icosapent ethyl: EPA only
- c. Omega-3 carboxylic acid: DHA and EPA
- 2. Efficacy
- a. Lowers TG by 26%–45%
- b. Can raise LDL-C when TG concentrations are high
- c. Raises HDL-C by 5%–14%
- 3. Mechanism of action: Reduction of hepatic production of very-low-density lipoproteins; possible reduction in hepatic synthesis of TG; increased hepatic β-oxidation
- 4. Adverse effects: Arthralgia, GI effects (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, bleeding (because of inhibition of platelet aggregation)
- 5. Dose: 2–4.8 g/day as a single dose or in two divided doses

Lomitapide

- **1. Efficacy: Lowers LDL-C by about 45%**
- **2. Mechanism of action: Selective microsomal TG protein inhibitor. Microsomal triglyceride transfer protein (MTP) is a member of a group of proteins that are able to transfer of lipids between membranes.**
- **3. Indicated for Homozygous Familial Hypercholesterolemia (HoFH)**
- **4. Adverse effects and monitoring: Hepatotoxicity, teratogenicity, GI symptoms; monitor LFTs at baseline, then monthly for 1 year (and before increasing dose), then every 3 months (and before increasing dose); female patients also need to have a negative pregnancy test before initiating therapy**
- **5. To reduce incidence of fat-soluble nutrient deficiency, administer daily supplements containing vitamin E (400 units), linoleic acid (≥200 mg), alpha-linolenic acid (≥210 mg), EPA (≥110 mg), and DHA (≥80 mg).**
- **6. Contraindications: Pregnancy, concurrent use of moderate or strong CYP3A4 inhibitors, moderate or severe hepatic disease**
- **7. Drug interactions**
- **a. Major CYP3A4 substrate**
- **b. Contraindicated with moderate and strong CYP3A4 inhibitors. Do not exceed 30 mg daily when used concomitantly with weak CYP3A4 inhibitors (e.g., atorvastatin, oral contraceptives).**
- **8. Dose: 5 mg once daily, can be titrated to 60 mg/day**

Apo B Antisense Oligonucleotides (Mipomersen)

- **1. Mipomersen is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apo B-100. This action leads to reduced apo B synthesis, the structural core for all atherogenic lipids, including LDL-C.**
- **2. Mipomersen is administered via subcutaneous injection. The drug has a bioavailability ranging from 54% to 78%. Peak plasma concentrations are generally obtained within 3 to 4 hours.**
- **3. Mipomersen is indicated as an adjunct therapy to a low-fat diet and other lipid lowering agents to reduce LDL-C, ApoB, TC, and non-HDL in patients with HoFH.**
- **4. Maximum LDL-C reduction is usually seen after approximately 6 months of therapy.**


Thank
You!

Fluid & Electrolyte Imbalance

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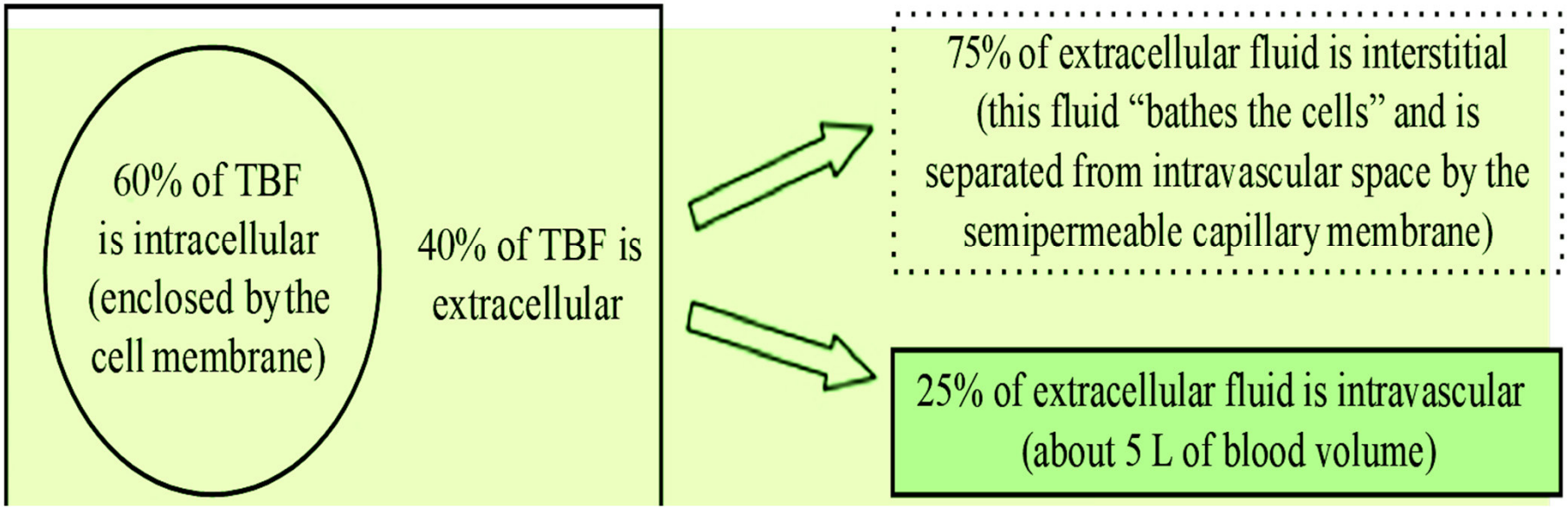
Distribution of total body fluid (TBF)

- **Help maintain body temperature and cell shape**
- **Helps transport nutrients gases and wastes**



Distribution of intravenous fluid

- **Crystalloids (0.9% sodium chloride or lactated Ringer solution) are recommended for fluid resuscitation in hypovolemia.**
- **a. Na and Cl– do not freely cross into cells, but they will distribute evenly in the EC space.**
- **b. For 0.9% sodium chloride or lactated Ringer solution, only 25% remains in the intravascular space, and 75% distributes in the IS space; therefore, when 1 L of 0.9% sodium chloride or lactated Ringer solution is administered, about 250 mL of fluid remains in the intravascular compartment.**

Distribution of intravenous fluid

- 2. D5W is isosmotic and, because of rapid metabolism, it has the net effect of administering “free” water.
- a. D5W is metabolized to water and carbon dioxide.
- b. Water can cross any membrane in the body; therefore, it is evenly distributed in TBF (“free” because it is free to cross any membrane).
- i. Many experts avoid administering D5W whenever possible in patients with neurologic injury and elevated intracranial pressure (ICP) because it can cross into cerebral cells, causing further elevation in ICP.
- ii. Some practitioners avoid the use of D5W because of the risk of hyperglycemia, although D5W contains only 5 g of dextrose/100 mL, which is equivalent to 17 kcal/100 mL.

Distribution of intravenous fluid

- c. For D5W, 60% distributes to the IC space and 40% distributes to the EC space. Of the 40% distributed to the EC space, 25% remains in the intravascular space, and 75% distributes to the IS space. Therefore, when 1 L of D5W is administered intravenously, about 100 mL of fluid remains in the intravascular compartment.
- 3. Colloids include packed red blood cells, pooled human plasma (5% albumin, 25% albumin, and 5% plasma protein fraction), semisynthetic glucose polymers (dextran), and semisynthetic hydroxyethyl starch (hetastarch).
- a. Colloids are too large to cross the capillary membrane; therefore, they remain primarily in the intravascular space (although a small portion "leaks" into the IS space).

Distribution of intravenous fluid

- **b. Except for 25% albumin, administering 500 mL of colloid results in a 500-mL intravascular volume expansion.**
- **c. Because 25% albumin has an oncotic pressure about 5-fold that of normal plasma, it causes a fluid shift from the IS space into the intravascular space. For this reason, 100 mL of 25% albumin results in around 500 mL of intravascular volume expansion. This hyperoncotic solution should generally be avoided in patients requiring fluid resuscitation, because although the intravascular space expands, fluid shifts out of the IS space, potentially causing dehydration. It may be useful in patients who do not require fluid resuscitation but who could benefit from a redistribution of fluid (e.g., ascites, pleural effusions).**
- **d. Hydroxyethyl starch and dextran products have been associated with coagulopathy and kidney impairment. In addition to acute kidney injury, hydroxyethyl starch is associated with increased mortality in critically ill patients.**

Distribution of intravenous fluid

Intravenous Fluid	Infused Volume (mL)	Equivalent Intravascular Volume Expansion (mL)
Normal saline	1000	250
Lactated Ringer solution	1000	250
Normosol-R and Plasma-Lyte	1000	250
5% Dextrose	1000	100
Albumin 5%	500	500
Albumin 25%	100	500
Hydroxyethyl starch 6%	500	500

Fluid Resuscitation

- 1. Intravascular fluid depletion can occur because of shock (hypovolemic or septic shock), and it is associated with reduced cardiac function and organ hypoperfusion.
- 2. Signs or symptoms usually occur when about 15% (750 mL) of blood volume is lost (e.g., hemorrhage) or shifts out of the intravascular space (e.g., severe sepsis).

✓Tachycardia (HR > 100 beats/minute)

✓Hypotension (SBP < 80 mm Hg)

✓Orthostatic changes in HR or BP

✓Increased BUN/SCr ratio > 20:1

✓Dry mucous membranes

✓ Decreased skin turgor

✓Reduced urine output

✓Dizziness

- Improvement in HR and BP after a 500- to 1000-mL fluid bolus

Fluid Resuscitation

- 3. Fluid resuscitation is indicated for patients with signs or symptoms of intravascular volume depletion.
- 4. The goal of fluid resuscitation is to restore intravascular volume and to prevent organ hypoperfusion.
- 5. Because intravascular volume depletion can cause organ dysfunction and death, prompt resuscitation is necessary.
- a. Intravenous fluids are infused rapidly, preferably through a large-bore catheter.
- b. Intravenous fluids are administered as a 500- to 1000-mL bolus, (30 mg/kg in septic patients) after which the patient is reevaluated; this process is continued as long as signs and symptoms of intra- vascular volume depletion are improving.

Fluid Resuscitation

- 6. Crystalloids (0.9% sodium chloride or lactated Ringer solution) are recommended for fluid resuscitation in hypovolemia.
- a. Lactated Ringer solution is historically preferred in surgery and trauma patients, but no evidence suggests superiority over normal saline for fluid resuscitation in these settings.
- b. The lactate in lactated Ringer solution is metabolized to bicarbonate, and it can theoretically be useful for metabolic acidosis; however, lactate metabolism is impaired during shock. Thus, lactated Ringer solution may be an ineffective source of bicarbonate.
- c. Lactated Ringer solution has been considered to provide a more physiologic amount of Cl (109 mmol/L) than 0.9% sodium chloride (154 mmol/L). A balanced fluid regimen (e.g., lactated Ringer solution, Plasma-Lyte 148) was associated with a reduction in the incidence of acute kidney injury compared with a standard regimen (e.g., 0.9% sodium chloride, colloids containing Cl 120–130 mmol/L).

Content of Common Crystalloid Solutions

	Contents (mEq/L)	Osmolarity (mOsmol/L)
Sodium chloride 0.9% (NS)	Na 154 Cl 154	310
Lactated Ringer (LR)	Na 130 Cl 109 K 4 Ca 3 Lactate 28	273
Normosol-R	Na 140 Cl 98 K 5 Mg 3 Acetate 27/Gluconate 23	295

Maintenance intravenous fluids

- 1. Maintenance intravenous fluids are indicated in patients who are unable to tolerate oral fluids.
- 2. The goal of maintenance intravenous fluids is to prevent dehydration and to maintain a normal fluid and electrolyte balance.
- 3. Maintenance intravenous fluids are typically administered as a continuous infusion through a peripheral or central intravenous catheter.
- 4. Common methods of estimating the daily volume in children and adults:
- a. Administer 100 mL/kg for first 10 kg, followed by 50 mL/kg for the next 10–20 kg (i.e., 1500 mL for the first 20 kg) plus 20 mL/kg for every kilogram greater than 20 kg or
- b. Administer 20–40 mL/kg/day (for adults only).
- Total daily maintenance fluid requirements = 1500 ml + {20 ml/kg X [weight (kg)-20]}

Maintenance intravenous fluids

- c. For elderly patients (eg, greater than 60 years old), use 15 mL/kg for every kilogram above 20 kg.
- d. Note: Infusion rate = total fluid volume per day ÷ 24 hour
- e. Administer half the calculated fluid during the first 8 hr, first subtracting any boluses from this amount, Administer the remainder over the next 16 hr
- 5. A typical maintenance intravenous fluid is D5W with 0.45% sodium chloride plus 20–40 mEq of potassium chloride per liter. The potassium chloride content can be adjusted for the individual patient.
- 6. When an infusion of 150 mEq of sodium bicarbonate per liter is indicated, it is recommended to add sodium bicarbonate to D5W or sterile water for injection instead of 0.9% sodium chloride.

OSMOLALITY

- **A. Plasma osmolality is normally 275–290 mOsm/kg.**
- **1. Terminology**
- **a. Osmolality is a measure of the osmoles of solute per kilogram of solvent (Osm/kg), whereas osmolarity is a measure of osmoles of solute per liter of solution (Osm/L).**
- **b. Plasma osmolarity (mOsm/L) can be calculated as osmolality × 0.995, showing that there is no clinically significant difference between them (i.e., plasma osmolarity is about 1% lower than plasma osmolality).**
- **2. Plasma osmolality is maintained within a normal range by thirst and secretion of arginine vasopressin (i.e., antidiuretic hormone [ADH]) from the posterior pituitary.**

OSMOLALITY

- **A. Plasma osmolality is normally 275–290 mOsm/kg.**
- **3. Sodium salts are the primary determinant of plasma osmolality, and they regulate fluid shifts between the IC and EC fluid compartments.**
- **4. Plasma osmolality (in milliosmoles per kilogram) can be estimated: (2 × Na+ mEq/L) + (glucose mg/dL/18) + (BUN mg/dL) ÷ 2.8.**
- **5. Increases in plasma osmolality cause an osmotic shift of fluid into the plasma, resulting in cellular dehydration and shrinkage.**
- **6. Decreases in plasma osmolality cause an osmotic shift of fluid into cells, resulting in cellular over- hydration and swelling.**

OSMOLALITY

- **B. Intravenous fluids can be classified by their osmolarity relative to plasma.**
- **1. Isotonic fluid does not result in a fluid shift between fluid compartments because the osmolarity is similar to plasma.**
- **2. Hypertonic fluid, such as NaCl 3%, can cause fluid to shift from the IC to the EC compartment, with subsequent cellular dehydration and shrinkage.**
- **Hypertonic saline is used in traumatic brain injury to reduce an elevated Intracranial pressure (ICP) and thereby increase cerebral perfusion pressure. It is typically used if sustained ICP is greater than 20 mm Hg as measured with an ICP monitor.**
- **Hypertonic saline is used for symptomatic hyponatremia.**

OSMOLALITY

- **B. Intravenous fluids can be classified by their osmolarity relative to plasma.**
- **3. Hypotonic fluid, such as NaCl 0.225%, with an osmolarity less than 150 mOsm/L can cause fluid to shift from the EC to the IC compartment, with subsequent cellular overhydration and swelling.**
- **a. Red blood cell swelling can cause cell rupture (i.e., hemolysis).**
- **b. Brain cells can swell, causing cerebral edema and herniation; this is most likely to occur with acute hyponatremia (occurring in less than 2 days).**

Hyponatremia and hypo-osmolal states

- A. Sodium salts are the primary determinants of plasma osmolality (and subsequent fluid shifts between the IC and EC compartments).
- 1. A reduction in serum sodium of less than 136 mEq/L usually correlates with a reduction in plasma osmolality.
- 2. Hyponatremia with subsequent hypo-osmolality causes fluid to shift into cells (cellular overhydration).
- Hypotonic hyponatremia can be divided into three types according to volume status.

Hyponatremia and hypo-osmolal states

- **3. In select cases, hyponatremia is associated with either a normal or an elevated plasma osmolality.**
- **a. This is known as pseudohyponatremia, because Na+ content in the body is not actually reduced. Instead, Na+ shifts from the EC compartment into the cells in an attempt to maintain plasma osmolality in a normal range. Another adaptation to increased plasma osmolality is the shift of water from inside cells to the EC compartment, which further dilutes the Na+ concentration.**
- **i. Severe hyperlipidemia can be associated with a normal or elevated plasma osmolality.**
- **ii. Severe hyperglycemia (i.e., during diabetic ketoacidosis) is associated with an elevated plasma osmolality.**
- **b. Once the underlying condition is corrected, Na+ will shift out of the cells, and hyponatremia will resolve.**

Classification of Hyponatremia

	Hypovolemic Hyponatremia	Euvolemic Hyponatremia	Hypervolemic Hyponatremia
Description	Deficit of both Na+ and fluid, but total Na+ is decreased more than total body water	Normal total body Na+ with excess fluid volume (i.e., dilutional)	Excess Na+ and fluid, but fluid excess predominates
Example	Fluid loss (e.g., emesis, diarrhea, fever), third spacing, renal loss (diuretics), cerebral salt wasting	syndrome of inappropriate secretion of antidiuretic hormone (SIADH), medications	Heart failure, cirrhosis, nephrotic syndrome
Diagnosis	Urine Na+ < 25 mEq/L indicates nonrenal loss of Na+ (e.g., emesis, diarrhea); urine Na+ > 40 mEq/L indicates renal loss of Na+	Urine osmolality > 100 mOsm/kg (indicates impaired water excretion in presence of plasma osmolality < 275 mOsm/kg); urine sodium > 40 mEq/L	Urine Na+ < 25 mEq/L indicates edematous disorders (i.e., heart failure, cirrhosis, nephrotic syndrome); urine Na+ > 25 mEq/L indicates acute or chronic renal failure
Treatment	Fluid resuscitation	If drug-induced SIADH, remove offending agent; fluid restriction; demeclocycline; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), some institutions use urea	Sodium and water restriction; treat underlying cause; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), diuretics

Causes of hyponatremia

- 1. Replacement of lost solute with water
- a. Loss of solute (e.g., vomiting, diarrhea) usually involves the loss of isotonic fluid; therefore, alone, it will not cause hyponatremia.
- b. After the loss of isotonic fluid, hyponatremia can develop when the lost fluid is replaced with water.
- c. A common cause of hyponatremia in hospitals is the postoperative administration of hypotonic fluid.
- 2. Volume depletion and organ hypoperfusion stimulate ADH secretion to increase water reabsorption in the collecting tubules, potentially causing hyponatremia.
- 3. SIADH and cortisol deficiency are both related to the excessive release of ADH.
- 4. Medications, including thiazide diuretics, antiepileptic drugs (e.g., carbamazepine, oxcarbazepine), and antidepressants (especially selective serotonin reuptake inhibitors but also tricyclic antidepressants), can cause hyponatremia. Drug-induced hyponatremia is more likely to occur in older adults and in those who drink large volumes of water.
- 5. Renal failure impairs the ability to excrete dilute urine, predisposing to hyponatremia.

Symptoms of hyponatremia

Serum Sodium (mEq/L)	Clinical Manifestations
120–125	Nausea, malaise
115–120	Headache, lethargy, obtundation, unsteadiness, confusion
< 115	Delirium, seizure, coma, respiratory arrest, death

Treatment of hyponatremia

- 1. Treat underlying cause.
- 2. Raise serum sodium at a safe rate, defined as a change no greater than 10–12 mEq/L in 24 hours.
- 3. Treatment depends on volume status, the presence and severity of symptoms, and the onset of hyponatremia.
- a. If the patient is euvolemic or edematous, there are two treatment options:
- i. Fluid restriction (to less than 800 mL/day) is the typical first-line recommendation for asymptomatic patients. Note that sodium administration is not recommended for asymptomatic patients because it can worsen edema.
- ii. Vasopressin antagonists (e.g., intravenous conivaptan, oral tolvaptan) can be used in euvolemic (i.e., SIADH) or hypervolemic (i.e., heart failure) patients to promote aquaresis, increase serum sodium, alleviate symptoms, and reduce weight.

Treatment of hyponatremia

- **b. If the patient has intravascular volume depletion, volume must be replaced first with intravenous crystalloids (e.g., 0.9% sodium chloride).**
- **i. Until intravascular volume is restored, the patient will continue to secrete ADH, causing water reabsorption and subsequent hyponatremia.**
- **ii. Once intravascular volume is restored, ADH secretion will decrease, causing water to be excreted. This can lead to a rapid correction of serum sodium; careful monitoring is necessary to prevent overly rapid correction.**
- **iii. Volume status can be assessed by skin turgor, jugular venous pressure, and urine sodium.**

Treatment of hyponatremia

- **d. Patients with symptomatic hyponatremia should be treated with hypertonic saline.**
- **4. Correct hypokalemia, if present, with hyponatremia.**
- **a. Hypokalemia will cause a reduction in serum sodium because Na+ enters cells to account for the reduction in IC K+ to maintain cellular electroneutrality.**
- **b. Administration of K+ will correct hyponatremia.**
- **c. Use caution when giving K+ to prevent overly rapid correction of serum sodium.**

Hypernatremia and hyperosmolal states

- **A. Hyperosmolality with serum sodium greater than 145 mEq/L**
- **1. The osmotic gradient associated with hypernatremia causes water movement out of cells and into the EC space.**
- **2. Symptoms are related primarily to the dehydration of brain cells.**
- **B. Causes of hypernatremia**
- **1. Loss of water because of fever, burns, infection, renal loss (e.g., diabetes insipidus), gastrointestinal (GI) loss**
- **2. Retention of Na+ because of the administration of hypertonic saline or any form of Na+**
- **3. Certain neurologic injuries receive hypertonic saline to target a higher sodium goal**

HYPERNATREMIA AND HYPEROSMOLAL STATES

- **C. Prevention of hypernatremia through osmoregulation**
- **1. Plasma osmolality is maintained at 275–290 mOsm/kg, despite changes in water and Na+ intake.**
- **2. Hypernatremia is prevented first by the release of ADH, causing water reabsorption.**
- **3. Hypernatremia is also prevented by thirst.**
- **a. Hypernatremia occurs primarily in adults with altered mental status who have an impaired thirst response or do not have access to or the ability to ask for water.**
- **b. Hypernatremia can also occur in infants.**

HYPERNATREMIA AND HYPEROSMOLAL STATES

- **D. Cerebral osmotic adaptation**
- **1. Similar to patients with hyponatremia, patients with chronic hypernatremia can have cerebral osmotic adaptation.**
- **a. Brain cells take up solutes, Na+, and K+, thus limiting the osmotic gradient between the IC and EC fluid compartments.**
- **b. This prevents cellular dehydration, and it will increase the brain volume toward a normal value, despite hypernatremia.**
- **2. Because of osmotic adaptation, patients with chronic hypernatremia may be asymptomatic.**

Hypernatremia and hyperosmolal states

- **E. Symptoms of hypernatremia are primarily neurologic.**
- **1. Similar to hyponatremia, the symptoms of hypernatremia are related to the rate of increase in plasma osmolality and the degree of increase in plasma osmolality.**
- **2. Earlier symptoms include lethargy, weakness, and irritability.**
- **3. Symptoms can progress to twitching, seizures, coma, and death if serum sodium is greater than 158 mEq/L.**
- **4. Cerebral dehydration can cause cerebral vein rupture with subsequent intracerebral or subarachnoid hemorrhage.**

Treatment of hypernatremia

- 1. Rapid correction of chronic hypernatremia can result in cerebral edema, seizure, permanent neurologic damage, and death.
- a. With osmotic adaptation, the brain volume is raised toward normal despite an elevated serum osmolarity.
- b. Osmotic adaptation combined with a rapid reduction in plasma osmolality can cause an osmotic gradient, causing water to move into brain cells with subsequent cerebral edema.
- 2. In patients with symptomatic hypernatremia, serum sodium should be reduced slowly by no more than 0.5 mEq/L/hour or 12 mEq/L/day.
- 3. Treat hypernatremia by replacing water deficit slowly over several days to prevent overly rapid correc- tion of serum sodium.
- a. Using LBW, the estimated water deficit (in liters) is (0.4 × LBW) × [(Serum sodium/140) − 1] in women (multiply LBW by 0.5 in men).

Treatment of hypernatremia

- **4. Administer free water orally or intravenously as D5W.**
- **5. If concurrent Na+ and water depletion occur (e.g., vomiting, diarrhea, diuretic-induced depletion), use a combination of D5W and 0.225% sodium chloride.**
- **6. If the patient is hypotensive because of volume depletion, first restore intravascular volume with 0.9% sodium chloride to restore tissue perfusion. Normal saline is the preferred crystalloid for fluid resuscitation, and it is still relatively hypotonic in the patient with hypernatremia.**
- **7. Patients with severe central diabetes insipidus may require desmopressin (DDAVP) (a synthetic analog of ADH) to replace insufficient or absent endogenous ADH. Diabetes insipidus is marked by increased urine output and decreased urine specific gravity.**

DISORDERS OF K+

- A. Normal plasma potassium concentrations are 3.5–5 mEq/L.
- B. K+ is the primary IC cation (maintains electroneutrality with Na, the primary EC cation).
- C. K+ balance is maintained between the IC and EC compartments by several factors, including the following:
- 1. β -Adrenergic stimulation (caused by epinephrine) promotes cellular uptake of K+.
- 2. Insulin promotes cellular uptake of K+.
- 3. Plasma potassium concentration directly correlates with movement of K+ in and out of cells because of passive shifts based on the concentration gradient across the cell membrane.
- D. Normal plasma concentrations of K+ are maintained by renal excretion.
- E. Hypokalemia (K+ concentration less than 3.5 mEq/L)

Causes of hypokalemia

- a. Reduced intake seldom causes hypokalemia, because renal excretion is minimized because of increased renal tubular absorption.
- b. Increased shift of K+ into cells can occur with the following:
- i. Alkalosis
- ii. Insulin or a carbohydrate load
- iii. β2-Receptor stimulation caused by stress-induced epinephrine release or administration of a β-agonist (e.g., albuterol, dobutamine)
- iv. Hypothermia

Causes of hypokalemia

- **c. Increased GI losses of K+ can occur with vomiting, diarrhea, intestinal fistula or enteral tube drain- age, and chronic laxative abuse.**
- **d. Increased urinary losses can occur with mineralocorticoid excess (e.g., aldosterone) and diuretic use (e.g., loop and thiazides).**
- **e. Hypomagnesemia is commonly associated with hypokalemia caused by increased renal loss of K+; correction of plasma potassium requires simultaneous correction of serum magnesium.**

Symptoms of hypokalemia

- **2. Symptoms of hypokalemia generally occur when plasma potassium is less than 3 mEq/L and can include the following:**
- **a. Muscle weakness occurs most commonly in the lower extremities.**
- **b. ECG changes (flattened T waves or elevated U wave) occur.**
- **c. Cardiac arrhythmias (bradycardia, heart block, ventricular tachycardia, ventricular fibrillation) occur.**
- **d. Rhabdomyolysis can occur because hypokalemia can cause reduced blood flow to skeletal muscle.**

Treatment of hypokalemia

- **3. Treatment of hypokalemia**
- **a. K+ deficit can be estimated as 200–400 mEq of K+ for every 1 mEq/L reduction in plasma potassium.**
- **b. Potassium chloride is the preferred salt in patients with concurrent metabolic alkalosis, because these patients typically lose Cl– through diuretics or GI loss. This is the most common presentation of hypokalemia.**
- **c. Potassium acetate can be administered intravenously, or potassium bicarbonate can be administered orally for patients with a metabolic acidosis that requires frequent K+ supplementation.**

Guidelines for administering K+

- i. Patients without ECG changes or symptoms of hypokalemia can be treated with oral supplementation.
- ii. Avoid mixing K+ in dextrose, which can cause insulin release with a subsequent IC shift of K+.
- iii. To avoid irritation, no more than about 60–80 mEq/L should be administered through a peripheral vein.
- iv. Recommended infusion rate is 10–20 mEq/hour to a maximum of 40 mEq/hour.
- v. Patients who receive K+ at rates faster than 10–20 mEq/hour should be monitored using a continuous ECG.

Plasma K+ (mEq/L)	Treatment	Comments
3–3.5	Oral KCl 40–80 mEq/day if no signs or symptoms (doses > 60 mEq should be divided to avoid GI adverse effects)	Recheck K+ daily
2.5–3	Oral KCl 120 mEq/day (in divided doses) or IV 60–80 mEq administered at 10–20 mEq/hr if signs or symptoms	Monitor K+ closely (i.e., 2 hr after infusion)
2–2.5	IV KCl 10–20 mEq/hr	Consider continuous ECG monitoring
< 2	IV KCl 20–40 mEq/hr	Requires continuous ECG monitoring

Hyperkalemia

- 1. Causes of hyperkalemia
- a. Increased intake
- b. Shift of K+ from the IC to the EC compartment causes hyperkalemia and can occur with the following:
- i. Acidosis
- ii. Insulin deficiency
- iii. β-Adrenergic blockade
- iv. Digoxin overdose
- v. Rewarming after hypothermia (e.g., after cardiac surgery)
- vi. Succinylcholine

Hyperkalemia

- **1. Causes of hyperkalemia**
- **c. Reduced urinary excretion can occur with:**
- **i. Kidney dysfunction**
- **ii. Intravascular volume depletion**
- **iii. Hypoaldosteronism**
- **iv. K+-Sparing diuretics, Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**
- **vi. Trimethoprim**

Symptoms of hyperkalemia

- a. Muscle weakness or paralysis is caused by changes in neuromuscular conduction; it typically occurs when plasma potassium exceeds 8 mEq/L.
- b. Abnormal cardiac conduction can first manifest as peaked, narrowed T waves (typically, when plasma potassium exceeds 6 mEq/L) and widening of the QRS, and it can progress to ventricular fibrillation and asystole.
- c. Not all patients will experience ECG changes, and the initial manifestation of hyperkalemia can be ventricular fibrillation; thus, consider emergency treatment even in patients with no ECG changes if plasma potassium exceeds 6.5 mEq/L.
- d. Conduction disturbances are increased by hypocalcemia, hyponatremia, acidosis, and rapid elevation in the plasma potassium concentration.

Pseudohyperkalemia

- 3. Pseudohyperkalemia should be considered if there is no apparent cause or symptoms of hyperkalemia.
- a. Can occur if K+ is released from cells while or after obtaining the blood specimen, usually because of trauma during venipuncture (hemolysis)
- b. Can result from measurement of the serum rather than the plasma potassium concentration; caused by K+ release during coagulation
- c. Contamination of blood specimen with potassium-containing intravenous fluids or parenteral nutrition

Treatment of hyperkalemia

- **a. Patients with an asymptomatic elevation in the plasma potassium who do not have signs or symptoms can be treated with a cation exchange resin (e.g., sodium polystyrene sulfonate) alone.**
- **b. Urgent and immediate treatment is required for patients with the following signs or symptoms:**
- **i. Plasma potassium greater than 6.5 mEq/L**
- **ii. Severe muscle weakness**
- **iii. ECG changes**

Treatment of hyperkalemia

- **c. Calcium should be administered intravenously to patients with symptomatic hyperkalemia to prevent hyperkalemia-induced arrhythmias, even if patients demonstrate normocalcemia.**
- **i. Calcium gluconate can be administered peripherally, and it is preferred to calcium chloride because of a reduced risk of tissue necrosis; dose is 10 mL (equivalent to 1 g, 90 mg elemental, or 4.65 mEq) of 10% calcium gluconate administered over 2–10 minutes. It can be repeated in 5 minutes if no improvement in ECG. Calcium chloride can be used if central intravenous access is available; however, the dose should be adjusted because 10 mL (1 g, 270 mg elemental, or 13.6 mEq) provides 3-fold the amount of elemental Ca as calcium gluconate.**
- **ii. Onset is within minutes, but duration is short (30–60 minutes).**
- **iii. It does not reduce plasma potassium, but it antagonizes the effect of K+ in cardiac conduction cells**
- **iv. Use in urgent circumstances while waiting for other measures (e.g., insulin and glucose) to lower plasma potassium.**
- **v. Use caution in patients receiving digoxin because hypercalcemia can precipitate digoxin toxicity, and there are reports of sudden death.**

Treatment of hyperkalemia

- d. The following treatment options are transient, causing a temporary shift of K+ from the EC fluid into the cells, and should be used for symptomatic hyperkalemia.
- i. Insulin and glucose
- (a) Dose is regular insulin 10 units intravenously plus 25–50 g of dextrose administered as a 50% dextrose intravenous push to prevent hypoglycemia.
- (b) Typically lowers plasma potassium by 0.5–1.5 mEq/L within 1 hour and may last for several hours
- (c) If patients have hyperglycemia, insulin alone can be administered.
- (d) Monitor for signs and symptoms of hypoglycemia even if dextrose is given

Treatment of hyperkalemia

- ii. Sodium bicarbonate
- (a) Dose is 50 mEq of intravenous sodium bicarbonate infused slowly over 5 minutes; it can be repeated after 30 minutes if needed.
- (b) It can lower plasma potassium within 30–60 minutes and persist for several hours.
- iii. β2-Adrenergic agonists (e.g., albuterol)
- (a) Dose is albuterol 10–20 mg nebulized over 10 minutes or 0.5 mg intravenously (not avail- able in the United States).
- (b) The dose will lower plasma potassium by 0.5–1.5 mEq/L.
- (c) Onset is within 30 minutes with inhalation.
- (d) Avoid use in patients with coronary ischemia because of the risk of tachycardia.
- (e) Consider use in combination with insulin.
- e. The previous treatment options should be followed by one of the following agents to remove excess K+ from the body.

Treatment of hyperkalemia

- **i. Diuretics**
- **(a) Loop or thiazide-type diuretics increase K+ renal excretion.**
- **(b) Ineffective in patients with advanced kidney disease**
- **ii. Cation exchange resins**
- **(a) Sodium polystyrene sulfonate exchanges Na+ for K+, resulting in GI excretion of K+. Exercise caution in patients with kidney disease or heart failure caused by Na+ (and sub- sequent fluid) retention.**
- **(b) Because of its slow onset (2 hours) and unpredictable efficacy, sodium polystyrene sulfonate is not indicated for emergency treatment of hyperkalemia.**
- **(c) A potassium binder was recently approved for use in hyperkalemia. As opposed to sodium polystyrene sulfonate, patiromer exchanges Ca2+ for K+, resulting in GI excretion of K+. As with other binders, caution should be used if patiromer is administered with other medications because it may reduce their absorption. Like sodium polystyrene sulfonate, patiromer should not be used for life-threatening hyperkalemia, because it has a slower onset of action. Another potassium-binding agent, sodium zirconium cyclosilicate, was also recently approved. It works by exchanging potassium for hydrogen and sodium.**

Treatment of hyperkalemia

- **iii. Dialysis**
- **(a) It is used when other measures are ineffective or when severe hyperkalemia is present.**
- **(b) Plasma potassium falls by more than 1 mEq/L in the first hour of dialysis and by about 2 mEq/L after 3 hours of dialysis.**
- **(c) Hemodialysis removes K+ faster than peritoneal dialysis.**
- **(d) Monitor for rebound increase in K+ after dialysis.**
- **(e) It is used in patients with advanced kidney disease**

DISORDERS OF MAGNESIUM HOMEOSTASIS

- A. Normal serum magnesium concentration is 1.7–2.3 mg/dL (1.4–1.8 mEq/L or 0.85–1.15 mmol/L).
- B. Hypomagnesemia (serum magnesium concentration less than 1.7 mg/dL)
- 1. Usually associated with impaired intestinal absorption (e.g., ulcerative colitis, diarrhea, pancreatitis, chronic laxative abuse), inadequate intake, hypokalemia, or increased renal excretion (e.g., diuretic use)
- a. Common in hospitalized patients
- b. Usually associated with alcoholism and delirium tremens
- 2. Often occurs concurrently with hypokalemia and hypocalcemia
- 3. Signs and symptoms
- a. Neuromuscular symptoms include tetany, twitching, and seizures.
- b. Cardiovascular symptoms include arrhythmias, sudden cardiac death, and hypertension.

DISORDERS OF MAGNESIUM HOMEOSTASIS

- **4. Treatment**
- **a. Oral supplements (e.g., magnesium oxide, magnesium-containing antacids) can be used for asymptomatic patients.**
- **b. Symptomatic patients should initially be treated with 1–4 g (8–32 mEq) of magnesium sulfate by slow intravenous infusion (about 1 g/hour to avoid hypotension or increased renal excretion because of rapid administration). Initial boluses can be followed by about 0.5 mEq/kg/day added to intravenous fluid and administered as a continuous infusion.**
- **c. Reduce the dose by half in patients with kidney insufficiency.**
- **d. About half of administered magnesium is excreted in the urine; therefore, magnesium replacement can occur over 3–5 days.**

Hypermagnesemia

- C. Hypermagnesemia (serum magnesium greater than 2.3 mg/dL)
- 1. Rarely occurs and is generally associated with chronic kidney disease
- 2. Signs and symptoms include nausea, vomiting, bradycardia, hypotension, heart block, asystole, respiratory failure, and death; signs and symptoms rarely occur unless magnesium concentration is greater than 4–5 mg/dL.
- 3. Treatment
- a. Discontinue all magnesium-containing medications.
- b. Asymptomatic patients with normal kidney function can be treated with 0.9% sodium chloride and loop diuretics.
- c. Symptomatic patients should be treated with 100–200 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes for cardiac stability.
- d. Hemodialysis may be needed for patients with kidney disease.

DISORDERS OF PHOSPHORUS HOMEOSTASIS

- A. Normal serum phosphorus concentration is 2.5–4.5 mg/dL.
- B. Hypophosphatemia (serum phosphorus concentration less than 3–3.5 mg/dL)
- 1. Causes of hypophosphatemia
- a. Increased renal elimination (e.g., diuretics, glucocorticoids, sodium bicarbonate)
- b. Rapidly refeeding patients with chronic malnutrition (“refeeding syndrome” in Parenteral Nutrition)
- c. Respiratory alkalosis
- d. Treatment of diabetic ketoacidosis; phosphorus shifts into the IC compartment as diabetic ketoacidosis is corrected

DISORDERS OF PHOSPHORUS HOMEOSTASIS

- **2. Signs and symptoms**
- **a. Tissue hypoxia can occur because of a decrease in oxygen release to peripheral tissues.**
- **b. Neurologic manifestations include confusion, delirium, seizures, and coma.**
- **c. Pulmonary and cardiac symptoms can include respiratory failure, difficulty weaning from mechanical ventilation, heart failure, and arrhythmias.**
- **d. Other organ systems affected include muscle, hematologic, bone, and kidney.**

DISORDERS OF PHOSPHORUS HOMEOSTASIS

- **3. Prevention and treatment**
- **a. Prevent hypophosphatemia by supplementing intravenous fluid with 10–30 mmol/L intravenous phosphorus in patients at risk of hypophosphatemia (e.g., malnourished, alcoholism, diabetic ketoacidosis).**
- **b. Oral phosphorus products (e.g., K-Phos Neutral; also contain K+ and Na) can be used for asymptomatic patients, but they are poorly absorbed.**
- **c. Symptomatic patients typically receive 15–30 mmol and sometimes up to 60 mmol (or 0.5–0.75 mmol/kg of IBW) of phosphorus (sodium phosphate or potassium phosphate) administered intravenously over 3–6 hours (maximum rate is 7.5 mmol/hour). Note Na+ content (4 mEq per 3 mmol of phosphate) and K+ content (4.4 mEq per 3 mmol of phosphate).**
- **4. Phosphate shortages**
- **a. Reserve phosphate products for patients who need them most (e.g., children, neonates, diabetic ketoacidosis, refeeding syndrome, critically ill patients).**
- **b. Intravenous fat emulsions contain 15 mmol/L as egg phospholipids; this may be sufficient phosphate for some patients.**

Hyperphosphatemia

- 1. It typically occurs in patients with chronic kidney disease or hypoparathyroidism.
- 2. In general, patients are asymptomatic, but they can have signs and symptoms including hypocalcemia, ECG changes, paresthesias, and vascular calcifications.
- 3. For treatment.
- a. reduce the amount of phosphate in your diet
- b. remove extra phosphate with dialysis
- c. A few drugs help reduce the amount of phosphate your intestines absorb from foods you eat. These include:
- i. calcium-based phosphate binders (calcium acetate and calcium carbonate)
- ii. lanthanum (Fosrenol)
- iii. Sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela)

DISORDERS OF CALCIUM HOMEOSTASIS

- **A. Normal serum calcium concentration is 8.5–10.5 mg/dL (total Ca^{2+} includes bound and unbound Ca^{2+}), and normal ionized calcium is 1.1–1.3 mmol/L (or 4.4–5.3 mg/dL).**
- **B. Distribution of Ca^{2+}**
- **1. EC fluid contains less than 1% of the total body stores of Ca^{2+}; 99% of total body stores of Ca^{2+} are in skeletal bone.**
- **a. About half of Ca^{2+} in the EC compartment is bound to plasma proteins (primarily albumin).**
- **b. The active form of Ca^{2+} is the unbound or ionized Ca^{2+}.**
- **2. Ionized Ca^{2+} is regulated by parathyroid hormone, phosphorus, vitamin D, and calcitonin.**

Hypocalcemia

- 1. It occurs in patients with chronic kidney disease, hypoparathyroidism, vitamin D deficiency, alcohol- ism, and hyperphosphatemia, and in patients receiving large amounts of blood products or patients undergoing continuous renal replacement therapy (CRRT) [i.e., Ca2+ chelates with citrate used as anticoagulation for plasmapheresis or CRRT])
- 2. Factors that cause an increase in EC Ca2+ binding to albumin (e.g., metabolic alkalosis) can cause a reduction in plasma ionized Ca2+ concentration, leading to symptomatic hypocalcemia.
- 3. A low serum albumin will cause a falsely low total serum calcium reading.
- 4. Signs and symptoms include tetany, muscle spasms, hypoactive reflexes, anxiety, hallucinations, lethargy, hypotension, and seizures.

DISORDERS OF CALCIUM HOMEOSTASIS

- **5. Treatment**
- **a. Asymptomatic hypocalcemia associated with hypoalbuminemia is typically associated with normal ionized Ca^{2+} concentrations and therefore does not require treatment.**
- **b. Asymptomatic hypocalcemia can be treated with oral Ca^{2+} supplements at a dose of 2–4 g/day of elemental Ca^{2+} in divided doses; patients may also require vitamin D supplementation.**
- **c. Symptomatic hypocalcemia is treated with 200–300 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes; this is sometimes followed by a continuous infusion.**
- **i. Equivalent to 1 g of calcium chloride (273 mg of elemental Ca^{2+}) administered through a central intravenous catheter; peripheral administration of calcium chloride can result in severe limb ischemia**
- **ii. Equivalent to 2–3 g of calcium gluconate (180–270 mg of elemental Ca^{2+}); preferred for peripheral intravenous administration**
- **iii. Do not infuse Ca^{2+} at a rate faster than 60 mg of elemental Ca^{2+} per minute; rapid administration, which is not recommended, is associated with hypotension, bradycardia, or asystole.**
- **iv. The duration of an intravenous dose of Ca^{2+} is ideally 1–2 hours. If a continuous infusion is used, the rate should be 0.5–2 mg/kg/hour of elemental Ca^{2+}.**

Hypercalcemia

- **D. Hypercalcemia (serum calcium concentration greater than 10.5 mg/dL) is usually related to malignancy or hyperparathyroidism.**
- **a. Calcitonin (Miacalcin). This hormone controls calcium levels in the blood. Mild nausea might be a side effect.**
- **b. Calcimimetics. This type of drug can help control overactive parathyroid glands. Cinacalcet (Sensipar) has been approved for managing hypercalcemia.**
- **c. Bisphosphonates. Intravenous osteoporosis drugs (Pamidronate and etidronate), which can quickly lower calcium levels, are often used to treat hypercalcemia due to cancer.**
- **d. Denosumab (Prolia, Xgeva). This drug is often used to treat people with cancer-caused hypercalcemia who don't respond well to bisphosphonates.**
- **e. Prednisone. If your hypercalcemia is caused by high levels of vitamin D, short-term use of steroid pills such as prednisone are usually helpful.**
- **f. IV fluids and diuretics. Extremely high calcium levels can be a medical emergency.**


Thank
You!

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Acute coronary syndromes

♣ DEFINITIONS

- Acute coronary syndromes (ACSs) include all clinical syndromes compatible with acute myocardial ischemia resulting from an imbalance between myocardial oxygen demand and supply.
- In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus.
- ACSs are classified according to electrocardiographic (ECG) changes into:
- ST-segment-elevation ACS (STE ACS or STEMI) and (2) non–ST segment- elevation ACS (NSTE ACS), which includes non–ST-segment elevation myocardial infarction (NSTE MI) and unstable angina (UA).
- After a STEMI, pathologic Q waves are seen frequently on the ECG and usually indicate trans mural MI. Non–Q-wave MI, which is seen predominantly in NSTE MI, is limited to the sub endcardial myocardium.
- NSTEMI differs from UA in that ischemia is severe enough to produce myocardial necrosis, resulting in release of detectable amounts of biochemical markers, primarily troponin I or T and creatine kinase myocardial band (CK-MB) from the necrotic myocytes into the bloodstream.

♣ PATHOPHYSIOLOGY

- The formation of atherosclerotic plaques is the underlying cause of coronary artery disease (CAD) and ACS in most patients. Endothelial dysfunction leads to the formation of fatty streaks in the coronary arteries and eventually to atherosclerotic plaques. Factors responsible for development of atherosclerosis include hypertension, age, male gender, tobacco use, diabetes mellitus, obesity, and dyslipidemia.
- The cause of ACS in more than 90% of patients is rupture, fissuring, or erosion of an unstable atheromatous plaque. Plaques most susceptible to rupture have an eccentric shape, thin fibrous cap, large fatty core, high content of inflammatory cells such as macrophages and lymphocytes, limited amounts of smooth muscle, and significant compensatory enlargement.
- A partially or completely occlusive clot forms on top of the ruptured plaque. Exposure of collagen and tissue factor induce platelet adhesion and activation, which promote release of adenosine diphosphate and thromboxane
- A2 from platelets. These produce vasoconstriction and potentiate platelet activation. A change in the conformation of the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges (the final common pathway of platelet aggregation).
- Simultaneously, activation of the extrinsic coagulation cascade occurs as a result of exposure of blood to the thrombogenic lipid core and endothelium, which are rich in tissue factor. This

pathway ultimately leads to the formation of a fibrin clot composed of fibrin strands, cross-linked platelets, and trapped red blood cells.

- Ventricular remodeling occurs after an MI and is characterized by changes in the size, shape, and function of the left ventricle that may lead to cardiac failure. Factors contributing to ventricular remodeling include neurohormonal factors (e.g., activation of the renin-angiotensin-aldosterone and sympathetic nervous systems), hemodynamic factors, mechanical factors, changes in gene expression, and modifications in myocardial matrix metalloproteinase activity and their inhibitors. This process may lead to cardiomyocyte hypertrophy, loss of cardiomyocytes, and increased interstitial fibrosis, which promote both systolic and diastolic dysfunction.
- Complications of MI include cardiogenic shock, heart failure, valvular dysfunction, various arrhythmias, pericarditis, stroke secondary to left ventricular (LV) thrombus embolization, venous thromboembolism, and LV free-wall rupture.

	Subjective Findings	**Objective Findings**	**Extent of Injury**
NSTE-ACS UA	Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion Pain usually starts in the retrosternal area and can radiate to either or both arms, neck, or jaw Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent Less common atypical symptoms[a] (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope	ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur No positive biomarkers for cardiac necrosis	No myocardial injury; partial occlusion of coronary artery
NSTEMI		ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur Positive biomarkers (troponin I or T elevation)	Myocardial injury; partial occlusion of coronary artery
STEMI	Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation	ST-segment elevation > 1 mm above baseline on ECG in two or more contiguous leads Positive biomarkers (troponin I or T elevation)	Myocardial necrosis; total occlusion of coronary artery

♣ CLINICAL PRESENTATION

- The predominant symptom of ACS is midline anterior chest discomfort (most often occurring at rest), severe new-onset angina, or increasing angina that lasts at least 20 minutes.
- The discomfort may radiate to the shoulder, down the left arm, to the back, or to the jaw.
- Accompanying symptoms may include nausea, vomiting, diaphoresis, or shortness of breath.
- Elderly patients, patients with diabetes, and women are less likely to present with classic symptoms.
- There are no specific features indicative of ACS on physical examination. However, patients with ACS may present with signs of acute heart failure or arrhythmias.

♣ DIAGNOSIS

- A 12-lead ECG should be obtained within 10 minutes of patient presentation.
- Key findings indicating myocardial ischemia or MI are ST-segment elevation, ST-segment depression, and T-wave inversion. These changes in certain groupings of leads help to identify the location of the involved coronary artery. The appearance of a new left bundle-branch block accompanied by chest discomfort is highly specific for acute MI. Some patients with myocardial ischemia have no ECG changes, so biochemical markers and other risk factors for CAD should be assessed to determine the patient's risk for experiencing a new MI or other complications.
- Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI. An evolving MI is defined as a typical rise and gradual fall in troponin I or T or a more rapid rise and fall of CK-MB. Typically, blood is obtained immediately and two additional times in the first 12 to 24 hours after presentation. An MI is identified if at least one troponin value or two CK-MB values are greater than the MI decision limit set by the hospital. Both troponins and CK-MB are detectable within 6hours of MI. Troponins remain elevated for up to 10 days, whereas CKMB returns to normal within 48 hours.
- Patient symptoms, past medical history, ECG, and troponin or CK-MB determinations are used to stratify patients into low, medium, or high risk of death or MI or likelihood of needing urgent coronary angiography and percutaneous coronary intervention (PCI).

♣ DESIRED OUTCOME

- Short-term goals of therapy include: (1) 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), (2) prevention of complications and death, (3) prevention of coronary artery reocclusion, (4) relief of ischemic chest discomfort, and (5) maintenance of normoglycemia.

♣ TEATMENT

☒ GENERAL APPROACH

- General treatment measures include hospital admission, oxygen administration if saturation is less 90%, continuous multilead ST-segment monitoring for arrhythmias and ischemia, glycemic control, frequent measurement of vital signs, bedrest for 12 hours in hemodynamically stable patients, use of stools softeners to avoid Valsalva maneuver, and pain relief.
- Blood chemistry tests that should be performed include potassium and magnesium (which may affect rhythm), glucose (which when elevated places the patient at higher risk for morbidity and mortality), serum creatinine (to identify patients who may need drug dosing adjustments), baseline complete blood cell count and coagulation tests (because most patients receive antithrombotic therapy, which increases bleeding risk), and fasting lipid panel. The fasting lipid panel should be drawn within the first 24 hours of hospitalization because values for cholesterol (an acute phase reactant) may be falsely low after that period.
- It is important to triage and treat patients according to their risk category
- Patients with STE ACS are at high risk of death, and efforts to reestablish coronary perfusion should be initiated immediately (without evaluation of biochemical markers).
- Patients with NSTE ACS who are considered to be at low risk (based on TIMI risk score) should have serial biochemical markers obtained. If they are negative, the patient may be admitted to a general medical floor with ECG telemetry monitoring, undergo a noninvasive stress test, or may be discharged.
- High-risk NSTE ACS patients should undergo early coronary angiography (within 24 to 48 hours) and revascularization if a significant coronary artery stenosis is found. Moderate-risk patients with positive biochemical markers typically also undergo angiography and revascularization, if indicated.
- Moderate-risk patients with negative biochemical markers may initially undergo a noninvasive stress test, with only those having a positive test proceeding to angiography.

☒ NONPHARMACOLOGIC THERAPY

- For patients with STE ACS, either fibrinolysis or primary PCI (with either balloon angioplasty or stent placement) is the treatment of choice for reestablishing coronary artery blood flow when the patient presents within3 hours of symptom onset. Primary PCI may be associated with a lower mortality rate than fibrinolysis, possibly because PCI opens more than 90% of coronary arteries compared with less than 60% opened with fibrinolytics. The risks of intracranial hemorrhage (ICH) and major bleeding are also lower with PCI than with fibrinolysis. Primary PCI is generally preferred if institutions have skilled interventional cardiologists and other necessary facilities, in patients with cardiogenic shock, in patients with contraindications to fibrinolytics, and in patients presenting with symptom onset more

than 3 hours prior.

- In patients with NSTE ACS, clinical practice guidelines recommend either PCI or coronary artery bypass grafting revascularization as an early treatment for high-risk patients, and that such an approach also be considered for moderate-risk patients. An early invasive approach results in fewer MIs, less need for revascularization procedures over the next year after hospitalization, and lower cost than the conservative medical stabilization approach.

☒ EARLY PHARMACOTHERAPY FOR ST-SEGMENTELEVATION

- According to the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines, early pharmacologic therapy should include: (1) intranasal oxygen (if oxygen saturation is less than 90%); (2) sublingual (SL) nitroglycerin (NTG); (3) aspirin; (4) a β-blocker; (5) unfractionated heparin (UFH) or enoxaparin; and (6) fibrinolysis in eligible candidates. Morphine is administered to patients with refractory angina as an analgesic and venodilator that lowers preload. These agents should be administered early, while the patient is still in the emergency department.
- An angiotensin-converting enzyme (ACE) inhibitor should be started within 24 hours of presentation, particularly in patients with left ventricular ejection fraction (LVEF) ≤40%, signs of heart failure, or an anterior wall MI, if there are no contraindications. IV NTG and β-blockers should be administered to selected patients without contraindications.

⌘ Fibrinolytic Therapy

- A fibrinolytic agent is indicated in patients with STE ACS presenting within 12 hours of the onset of chest discomfort who have at least 1 mm of STE in two or more contiguous ECG leads or a new left bundle-branch block. It should also be considered in patients with those findings and persistent symptoms of ischemia who present within 12 to 24 hours of symptom onset. Fibrinolysis is preferred over primary PCI in patients presenting within 3 hours of symptom onset when there would be a delay in performing primary PCI.
- It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.
- Absolute contraindications to fibrinolytic therapy include: (1) active internal bleeding; (2) previous ICH at any time; (3) ischemic stroke within 3 months; (4) known intracranial neoplasm; (5) known structural vascular lesion; (6) suspected aortic dissection; and (7) significant closed head or facial trauma within 3 months. Primary PCI is preferred in these situations.
- Patients with relative contraindications to fibrinolytics may receive therapy if the perceived risk of death from MI is higher than the risk of major hemorrhage. These situations include: (1) severe, uncontrolled hypertension (blood pressure [BP] greater than 180/110 mm Hg); (2) history of prior ischemic stroke longer than 3 months prior, dementia, or known intracranial

pathology not considered an absolute contraindication; (3) current anticoagulant use; (4) known bleeding diathesis; (5) traumatic or prolonged cardiopulmonary resuscitation or major surgery within 3 weeks; (6) noncompressible vascular puncture; (7) recent (within 2 to 4 weeks) internal bleeding; (8) pregnancy; (9) active peptic ulcer; (10) history of severe, chronic poorly controlled hypertension; and (11) for streptokinase, prior administration (>5 days) or prior allergic reactions.

- Practice guidelines indicate that a more fibrin-specific agent (alteplase, reteplase, tenecteplase) is preferred over the non–fibrin-specific agent streptokinase. Fibrin-specific agents open a greater percentage of infarct arteries, which results in smaller infarcts and lower mortality.
- 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).

✓ **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. The risk of ICH is higher with fibrin-specific agents than with streptokinase. However, the risk of systemic bleeding other than ICH is higher with streptokinase than with fibrin-specific agents.

⌘ **Aspirin**

- Aspirin should be administered to all patients without contraindications within the first 24 hours of hospital admission. It provides an additional mortality benefit in patients with STE ACS when given with fibrinolytic therapy.
- In patients experiencing an ACS, non–enteric-coated aspirin, 162 to 325 mg, should be chewed and swallowed as soon as possible after the onset of symptoms or immediately after presentation to the emergency department regardless of the reperfusion strategy being considered.
- A daily maintenance dose of 75 to 162 mg is recommended thereafter and should be continued indefinitely.
- For patients undergoing PCI and receiving stents, the recommended dose is 325 once daily for

at least 30 days with bare metal stents, for 3 months with a sirolimus-eluting stent, and for 6 months with a paclitaxel-eluting stent, followed by 75 to 162 mg once daily thereafter.

- Low-dose aspirin is associated with a reduced risk of major bleeding, particularly GI bleeding. Other GI disturbances (e.g., dyspepsia, nausea) are infrequent with low-dose aspirin. Ibuprofen should not be administered on a regular basis concurrently with aspirin because it may block aspirin's antiplatelet effects.

⌘ Thienopyridines

- **Clopidogrel** is recommended for patients with an aspirin allergy. A 300- to 600-mg loading dose is given on the first hospital day, followed by a maintenance dose of 75 mg daily. It should be continued indefinitely.
- 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.
- For patients undergoing primary PCI, clopidogrel is administered as a 300- to 600-mg loading dose followed by a 75 mg/day maintenance dose, in combination with aspirin 325 mg once daily, to prevent subacute stent thrombosis and long-term cardiovascular events.
- The most frequent side effects of clopidogrel are nausea, vomiting, and diarrhea (5% of patients). Thrombotic thrombocytopenia purpura has been reported rarely. The most serious side effect of clopidogrel is hemorrhage.
- **Ticlopidine** is associated with neutropenia that requires frequent monitoring of the complete blood cell count during the first 3 months of use. For this reason, clopidogrel is the preferred thienopyridine for ACS and PCI patients.

⌘ Glycoprotein IIb/IIIa Receptor Inhibitors

- **Abciximab** is a first-line GP IIb/IIIa inhibitor for patients undergoing primary PCI who have not received fibrinolytics. It should not be administered to STE ACS patients who will not be undergoing PCI.
- Abciximab is preferred over **eptifibatide** and **tirofiban** in this setting because it is the most widely studied agent in primary PCI trials.
- Abciximab, in combination with aspirin, a thienopyridine, and UFH (administered as an infusion for the duration of the procedure), reduces mortality and reinfarction without increasing the risk of major bleeding.
- The dose of abciximab is 0.25 mg/kg IV bolus given 10 to 60 minutes before the start of PCI, followed by 0.125 mcg/kg/min (maximum 10 mcg/ min) for 12 hours.
- GP IIb/IIIa inhibitors may increase the risk of bleeding, especially if given in the setting of recent (<4 hours) administration of fibrinolytic therapy. An immune-mediated thrombocytopenia occurs in about 5% of patients.

⌘ **Anticoagulants**

- **Unfractionated heparin (UFH)** is a first-line anticoagulant for STE ACS, both for medical therapy and PCI.
- UFH should be initiated in the emergency department and continued for at least 48 hours in patients who will receive chronic warfarin after acute MI. If a patient undergoes PCI, UFH is discontinued immediately after the procedure.
- If a fibrinolytic agent is administered, UFH is given concomitantly with alteplase, reteplase, and tenecteplase, but UFH is not administered with streptokinase because no benefit of combined therapy has been demonstrated.
- Rates of reinfarction are higher if UFH is not given with the fibrinselective agents. For STE ACS, the dose of UFH is 60 units/kg IV bolus (maximum 4,000 units) followed by a continuous IV infusion of 12 units/kg/hour (maximum 1,000 units/hour).
- The dose is titrated to maintain the activated partial thromboplastin time (aPTT) between 50 and 70 seconds. The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with fibrinolytics and at 4 to 6 hours in patients not receiving thrombolytics.
- Besides bleeding, the most frequent adverse effect of UFH is immunemediated thrombocytopenia, which occurs in up to 5% of patients.
- **Low-molecular-weight heparins** (LMWHs) may be an alternative to UFH in STE ACS. **Enoxaparin** may produce a modest benefit over UFH in reducing the risk of death or nonfatal MI. Enoxaparin has not been studied in the setting of primary PCI.

⌘ **Nitrates**

- Immediately upon presentation, one SL **NTG** tablet should be administered every 5 minutes for up to three doses to relieve chest pain and myocardial ischemia.
- Intravenous NTG should be initiated in all patients with an ACS who do not have a contraindication and who have persistent ischemic symptoms, heart failure, or uncontrolled high BP. The usual dose is 5 to 10 mcg/min by continuous infusion, titrated up to 200 mcg/min until relief of symptoms or limiting side effects (e.g., headache or hypotension). Treatment should be continued for approximately 24 hours after ischemia is relieved.
- NTG causes venodilation, which lowers preload and myocardial oxygen demand. In addition, arterial vasodilation may lower BP, thereby reducing myocardial oxygen demand. Arterial dilation also relieves coronary artery vasospasm and improves myocardial blood flow and oxygenation.
- Oral nitrates play a limited role in ACS because clinical trials have failed to show a mortality benefit for IV followed by oral nitrate therapy in acute MI. Therefore, other life-saving therapy, such as ACE inhibitors and β- blockers, should not be withheld.
- The most significant adverse effects of nitrates are tachycardia, flushing, headache, and hypotension. Nitrates are contraindicated in patients who have taken the oral phosphodiesterase-5 inhibitors sildenafil or vardenafil within the prior 24 hours or tadalafil

within the prior 48 hours.

⌘ β-Adrenergic Blockers

- If there are no contraindications, a β-blocker should be administered early in the care of patients with STE ACS (within the first 24 hours) and continued indefinitely.
- The benefits result from blockade of β1 receptors in the myocardium, which reduces heart rate, myocardial contractility, and BP, thereby decreasing myocardial oxygen demand. The reduced heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.
- Because of these effects, β-blockers reduce the risk for recurrent ischemia, infarct size, risk of reinfarction, and occurrence of ventricular arrhythmias.
- The usual doses of β-blockers are as follows:

✓ **Metoprolol**: 5 mg by slow (over 1 to 2 minutes) IV bolus, repeated every 5 minutes for a total initial dose of 15 mg. If a conservative regimen is desired, initial doses can be reduced to 1 to 2 mg. This is followed in 15 to 30 minutes by 25 to 50 mg orally every 6 hours. If appropriate, initial IV therapy may be omitted.

✓ **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. If appropriate, the initial IV therapy may be omitted.

✓ **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. The initial IV therapy may be omitted.

✓ **Esmolol**: Starting maintenance dose of 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 until the desired therapeutic response is obtained, limiting symptoms develop, or a dose of 0.2 mg/kg/min is reached. An optional loading dose of 0.5 mg/kg may be given by slow IV administration (2 to 5 minutes) for more rapid onset of action. Alternatively, the initial IV therapy may be omitted.

- The most serious side effects early in ACS are hypotension, bradycardia, and heart block. Initial acute administration of β-blockers is not appropriate for patients presenting with decompensated heart failure. However, therapy may be attempted in most patients before hospital discharge after treatment of acute heart failure. Diabetes mellitus is not a contraindication to β-blocker use. If possible intolerance to β-blockers is a concern (e.g., due to chronic obstructive pulmonary disease), a short-acting drug such as metoprolol or esmolol should be administered IV initially.

⌘ Calcium Channel Blockers

- In the setting of STE ACS, calcium channel blockers are reserved for patients who have contraindications to β-blockers. They are used for relief of ischemic symptoms only.

- Patients who had been prescribed calcium channel blockers for hypertension who are not receiving β-blockers and who do not have a contraindication should have the calcium channel blocker discontinued and a β-blocker initiated. Dihydropyridine channel blockers (e.g., nifedipine) have little benefit on clinical outcomes beyond symptom relief. The role of verapamil and diltiazem appears to be limited to symptom relief or control of heart rate in patients with supraventricular arrhythmias in whom β-blockers are contraindicated or ineffective.
- Patients with variant (Prinzmetal's) angina or cocaine-induced ACS may benefit from calcium channel blockers as initial therapy because they can reverse coronary vasospasm. β-Blockers generally should be avoided in these situations because they may worsen vasospasm through an unopposed β2-blocking effect on smooth muscle.

☒ EARLY PHARMACOTHERAPY FOR NON–ST-SEGMENTELEVATION

- Early pharmacotherapy for NSTE ACS is similar to that for STE ACS except that: (1) fibrinolytic therapy is not administered; (2) GP IIb/IIIa receptor blockers are administered to high-risk patients; and (3) there are no standard quality performance measures for patients with NSTE ACS with UA.

- Fibrinolytics are not indicated in any patient with NSTE ACS, even those who have positive biochemical markers that indicate infarction. The risk of death from MI is lower in these patients, and the hemorrhagic risks of fibrinolytic therapy outweigh the benefit.

☒ Secondary prevention after myocardial infarction

❋ DESIRED OUTCOME

- The long-term goals after MI are to: (1) control modifiable coronary heart disease (CHD) risk factors; (2) prevent development of systolic heart failure; (3) prevent recurrent MI and stroke; and (4) prevent death, including sudden cardiac death.

❋ PHARMACOTHERAPY

⌘ General Approach

- Pharmacotherapy that has been proven to decrease mortality, heart failure, reinfarction, or stroke should be started before hospital discharge for secondary prevention.
- The ACC/AHA guidelines suggest that after 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 lingual spray and instructions for use in case of recurrent ischemic chest discomfort.
- Clopidogrel should be considered for most patients, but the duration of therapy is individualized according to the type of ACS and whether the patient is treated medically or

undergoes stent implantation.

- All patients should receive annual influenza vaccination.
- Selected patients also should be treated with long-term warfarin anticoagulation.
- For all ACS patients, treatment and control of modifiable risk factors such as hypertension, dyslipidemia, and diabetes mellitus are essential.
- Aspirin decreases the risk of death, recurrent MI, and stroke after MI. All patients should receive aspirin indefinitely (or clopidogrel if there are aspirin contraindications). The risk of major bleeding from chronic aspirin therapy is approximately 2% and is dose related. Therefore, after an initial dose of 325 mg, chronic low doses of 75 to 81 mg are recommended unless a stent is placed.
- 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.
- Warfarin should be considered in selected patients after an ACS, including those with an LV thrombus, extensive ventricular wall motion abnormalities on cardiac echocardiogram, and a history of thromboembolic disease or chronic atrial fibrillation.
- After an ACS, patients should receive a β-blocker indefinitely, regardless of whether they have residual symptoms of angina. Therapy should continue indefinitely in the absence of contraindications or intolerance.
- 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.
- All patients should be prescribed a short-acting SL NTG or lingual NTG spray to relieve anginal symptoms when necessary. Chronic long-acting nitrates have not been shown to reduce CHD event after MI. Therefore, chronic long-acting oral nitrates are not used in ACS patients who have undergone revascularization unless the patient has chronic stable angina or significant coronary stenosis that was not revascularized.
- ACE inhibitors should be initiated in all patients after MI to reduce mortality, decrease reinfarction, and prevent the development of heart failure. Data suggest that most patients with CAD (not just those with ACS or heart failure) benefit from an ACE inhibitor.
- The dose should be low initially and titrated to the dose used in clinical trials if tolerated. Example doses include the following:
  - ✓ Captopril: 6.25 to 12.5 mg initially; target dose 50 mg two or three times daily.
  - ✓ Enalapril: 2.5 to 5 mg initially; target dose 10 mg twice daily.
  - ✓ Lisinopril: 2.5 to 5 mg initially; target dose 10 to 20 mg once daily.
  - ✓ Ramipril: 1.25 to 2.5 mg initially; target dose 5 mg twice daily or 10 mg once daily.

✓ Trandolapril: 1 mg initially; target dose 4 mg once daily.

- An angiotensin receptor blocker may be prescribed for patients with ACE inhibitor cough and a low LVEF and heart failure after MI. Example doses include the following:

✓ Candesartan: 4 to 8 mg initially; target dose 32 mg once daily.

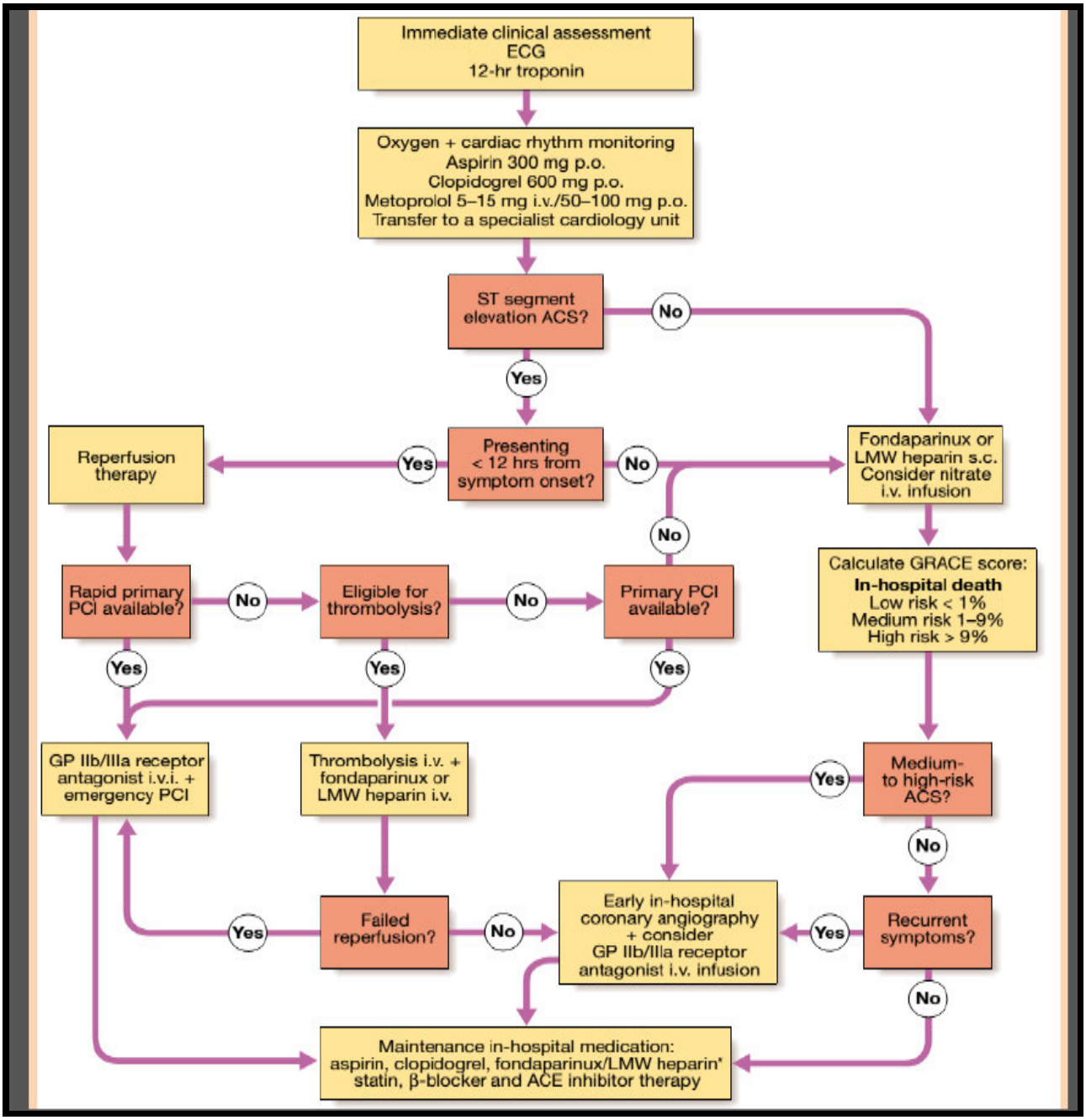
✓ Valsartan: 40 mg initially; target dose 160 mg twice daily.

- *Aldosterone Antagonists* either eplerenone or spironolactone should be considered within the first 2 weeks after MI to reduce mortality in all patients already receiving an ACE inhibitor who have LVEF ≤40% and either heart failure symptoms or a diagnosis of diabetes mellitus. The drugs are continued indefinitely. Example oral doses include the following:

✓ Eplerenone: 25 mg initially; target dose 50 mg once daily.

✓ Spironolactone: 12.5 mg initially; target dose 25 to 50 mg once daily.

- *Lipid-Lowering Agents:* All patients with CAD should receive dietary counseling and pharmacotherapy in order to reach a low-density lipoprotein (LDL) cholesterol concentration <100 mg/dL. Newer recommendations from the National Cholesterol Education Program give an optional LDL goal of <70 mg/dL in selected patients.
- Statins are the preferred agents for lowering LDL cholesterol and should be prescribed at or near discharge in most patients.
- A fibrate derivative or niacin should be considered in selected patients with a low high-density lipoprotein (HDL) cholesterol (<40 mg/dL) and/ or a high
- In the absence of contraindications, oral β-blockers should be administered to all patients with NSTE ACS. IV β-blockers should be considered in hemodynamically stable patients who present with persistent ischemia, hypertension, or tachycardia. The drugs are continued indefinitely.
- Calcium channel blockers should not be administered to most patients with ACS paclitaxel-coated stent.


Immediate clinical assessment
ECG
12-hr troponin
Oxygen + cardiac rhythm monitoring
Aspirin 300 mg p.o.
Clopidogrel 600 mg p.o.
Metoprolol 5–15 mg i.v./50–100 mg p.o.
Transfer to a specialist cardiology unit
ST segment elevation ACS?
No
Yes
Reperfusion therapy
Yes
Presenting < 12 hrs from symptom onset?
No
Fondaparinux or LMW heparin s.c.
Consider nitrate i.v. infusion
No
Rapid primary PCI available?
No
Eligible for thrombolysis?
No
Primary PCI available?
Calculate GRACE score:
In-hospital death
Low risk < 1%
Medium risk 1–9%
High risk > 9%
Yes
Yes
Yes
GP IIb/IIIa receptor antagonist i.v.i. + emergency PCI
Thrombolysis i.v. + fondaparinux or LMW heparin i.v.
Yes
Medium- to high-risk ACS?
No
Yes
Failed reperfusion?
No
Early in-hospital coronary angiography + consider GP IIb/IIIa receptor antagonist i.v. infusion
Yes
Recurrent symptoms?
No
Maintenance in-hospital medication:
aspirin, clopidogrel, fondaparinux/LMW heparin*
statin, β-blocker and ACE inhibitor therapy

Cardiac Arrhythmia

❑ SINUS RHYTHM

- Sinus rhythm refers to a normal phenomenon of mild acceleration and slowing of the heart rate that occurs with breathing in and out.
- The impulses are conducted from the SA node across the atria to the (AV) node and then down the bundle of Hiss to the Purkinje fibers and the ventricle. This is termed sinus rhythm

❖ ***The activity of the heart is controlled by:***

A- The sympathetic nervous system, which stimulates the SA node and penetrates most cardiac tissue

B- The parasympathetic verve, which reduces conduction through the AV node and slows the SA node

- Excessive Vagal stimulation results in bradycardia
- Anticholinergic drugs such as tricyclic antidepressants or atropine may remove Vagal control and cause tachycardia

❑ Definition of arrhythmia

- Arrhythmia is an abnormal cardiac rhythm, usually involving a change in rate or regularity, and is monitored by an electrocardiograph
- The term dysrhythmia is probably better since arrhythmia implies without rhythm.

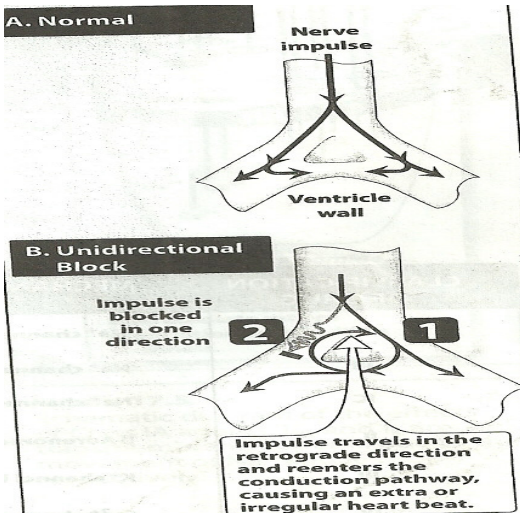
❑ General CAUSES OF ARRHYTHEMIAS

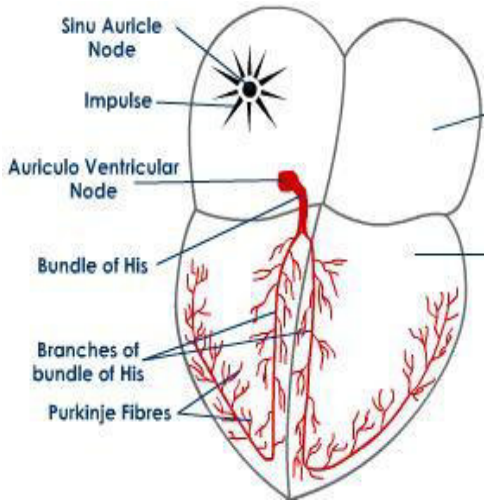
1. Abnormal automaticity or abnormal impulse formation

- The SA node shows the fastest rate of depolarization and exhibits a higher rate of discharges than that occurring in other pacemakers cells showing automaticity
- Thus the SA node normally acts as the pace of contraction of the myocardium and latent pacemakers are depolarized by impulses coming from SA node
- However , if other cardiac sites or other pacemakers show enhanced automaticity arrhythmia may occur
- Abnormal automaticity may also occur if myocardial cell are damaged as hypoxia, These cells may remain depolarised during diastole and therefore reach to firing threshold before normal cells and so abnormal automatic discharges occurs
- Automatic tachycardia is the classical examples of abnormal impulse formation arrhythmia
- Automatic tachycardia Caused *by* Digitalis glycoside, Catecholamine, Hypoxemia, Hypokalemia which may be caused by chronic use of thiazide-diuretics.
- Antiarrhythmics suppress automaticity by blocking either sodium or calcium channels

2. <u>Abnormal impulse conduction or re-entry arrhythmia</u>

- Impulses from higher pacemaker are normally conducted into down pathways that bifurcate to activate the entire ventricular surface
- A phenomenon called re-entry can occur if a unidirectional block caused by myocardial injury or prolonged refractory period result in abnormal conduction
- Unidirectional block makes the impulses to travel in retrograde direction to damaged or blocked area and then renter the point of bifurcation resulting in reexcitation or sustained or premature beats i.e. arrhythmia
- Re-entry is the most common cause of arrhythmias as atrial arrhythmia
- Antiarrhythmics prevent re-entry arrhythmia by slowing conduction





❑ **<u>Abnormal impulse formation or abnormal impulse conduction may be brought about in several ways.</u>**

1. An infarction may cause the death of pacemaker cells or conducting tissue
2. A cardiac tissue disorder, e.g. fibrosis or rheumatic fever, or a multi-
3. system connective tissue disorder, e.g. sarcoidosis, disrupts the conduction network
4. Sympathetic or parasympathetic control changes, e.g. stress, anxiety, exercise or smoking
5. Circulating drugs, e.g. antiarrhythmics or other substances, e.g. caffeine, alcohol, affect the heart directly or via the nervous system
6. Hypothyroidism, hyperthyroidism, hypoadrenalism, hyperkalemia and hypokalemia or other electrolyte disturbances
7. Patients who have pre-existing cardiac disorders including heart failure, hypertension or a recent infarction are at greater risk of arrhythmias
8. Older age is an independent risk factor and arrhythmias are also more common in pregnancy and following surgery.

❑ Signs and consequences of arrhythmias

- Dizziness or collapse because of a poor blood supply to the brain
- Shortness of breath because of poor oxygenation
- Angina associated with a poor coronary circulation and/or increased cardiac workload arising from a tachycardia
- Palpitations may be due to extra beats or the absence of a beat

❑ Diagnosis of arrhythemia

1- Signs and symptoms

- Dizziness - Shortness of breath - Chest pain & Palpitations

2- Intermittent 24-hour recordings of the ECG

- ECG is the most specific diagnostic tool, since signs and symptoms arrhythmias are not unique to arrhythmias.

❑ Types or description of arrhythmias

I. Bradyarrhythmias

- Sinus bradycardia
- Rhythm is Regular
- But Rate is less than 60 beats per minute
- Usually benign and often caused by patients on beta blockers

❋ **Bradycardia due to AV Block with varying degree**

A. First-degree AV block
B. Second-degree AV block
C. Third-degree AV block

I- Bradyarrhythmias

❖ ***Causes***

a. Metabolic disorder and tissue damage (hypoglycemia and brain injury) that lead to increased vagal tone
b. Decrease in sympathetic autonomic tone
c. Increase in parasympathetic tone mediated by the Vagus nerve
d. Changes in autonomic function caused by: Drugs such as verapamil or Deficiencies in thyroid

❖ ***Mechanism of Bradyarrhythmias***

- Increased Vagal tone causes AV block of varying degree which reduces the rate of impulses reaching the ventricles.
- AV block may be classified into three types

A. *First-degree AV block:*

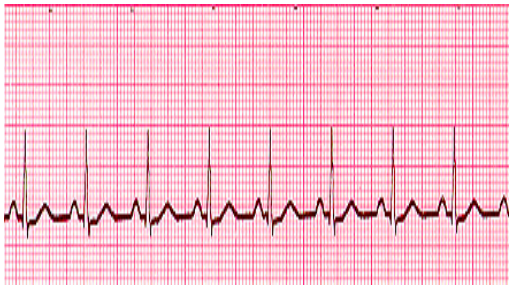
- All beats are conducted through the AV node, but with some delay.
- This does not require treatment but may be a warning to avoid drugs that would worsen the block, such as ß-blockers and class IV agents.

B- *Second-degree AV block*

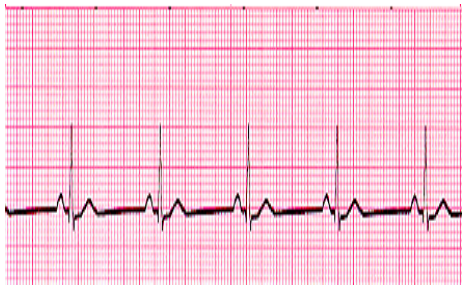
- Some, but not all, beats are conducted through the AV node.
- The need for treatment depends upon whether a satisfactory ventricular rate and output can be maintained

C- *Third-degree AV block*

- No conduction of sinus or atrial beats through the AV node
- Ventricles generate their own rhythm (escape rhythm)
- Requires treatment
- Sinus Bradycardia



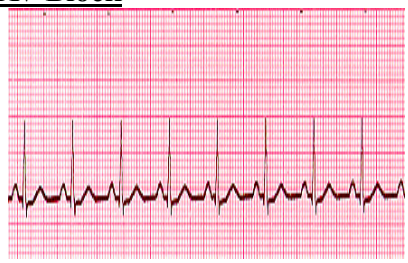
Sinus Rhythm



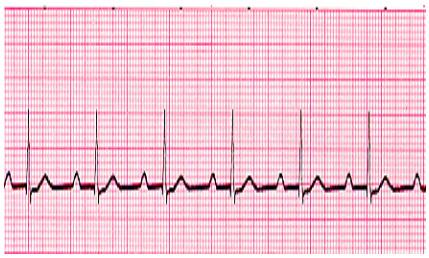
Sinus Bradycardia

- Rhythm - Regular
- Rate - less than 60 beats per minute
- QRS Duration - Normal
- P Wave - Visible before each QRS complex
- P-R Interval - Normal
- Usually benign and often caused by patients on beta blockers

❖ **1st Degree AV Block**



Sinus rhythm



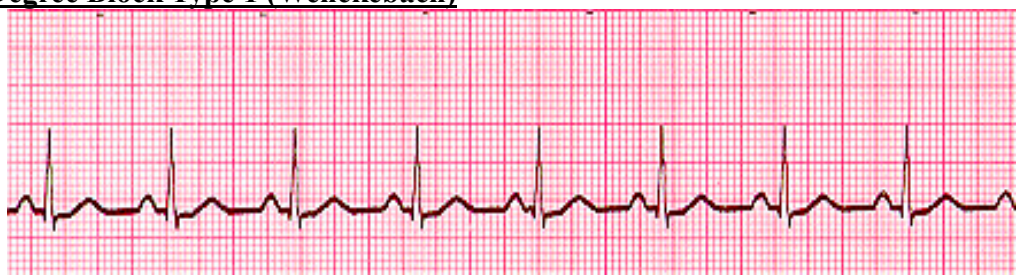
1st degree AV block

- 1st Degree AV block is caused by a conduction delay through the AV node but all electrical signals reach the ventricles.
- The normal P-R interval is between 0.12s to 0. 20s in length, or 3-5 small squares

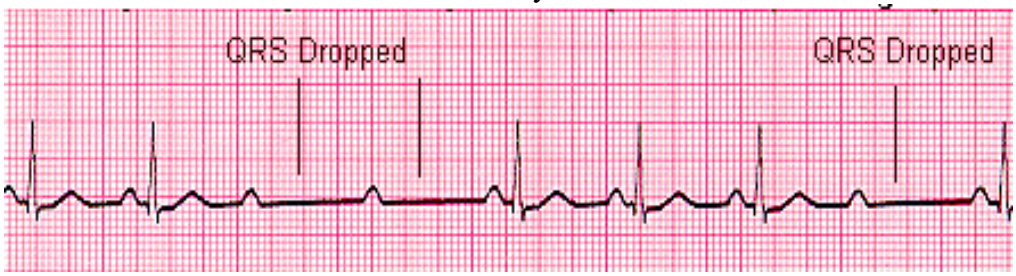
ECG

- Rhythm - Regular
- Rate - slow
- QRS Duration - Normal
- P Wave rate - Normal
- P-R Interval - Prolonged (> 5 small squares)

2nd Degree Block Type 1 (Wenckebach)



Sinus Rhythm



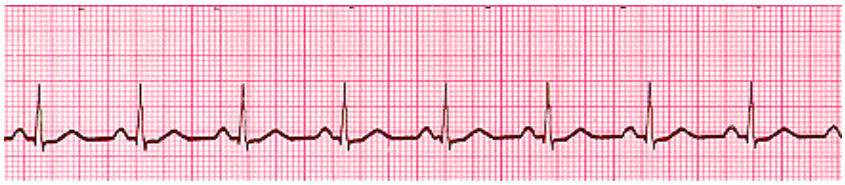
❖ **2nd degree AV block**

- Some but not all electrical excitation fails to pass through the A-V node
- Atrial contractions are not regularly followed by ventricular contraction or depolarization leading to some dropped QRS

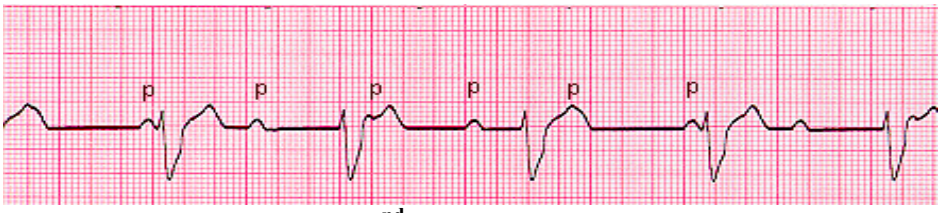
*** ECG:**

- Rhythm - Regular
- Rate - Normal or Slow
- QRS - Some dropped QRS
- P Wave rate - Normal
- P-R Interval - Normal or prolonged

❖ **3rd Degree Block**



Sinus Rhythm



3nd degree AV block

- 3rd degree block or complete heart block occurs when atrial contractions are 'normal' but no electrical conduction is conveyed to the ventricles
- The ventricles then generate their own signal through an 'escape mechanism' called escape beats which are 'slow

• **ECG :**

- Rhythm - Regular
- Rate -Slow
- QRS Duration – characteristic to ventricle own signal or escape beat
- P Waves - Unrelated
- P- R Interval - Variation

❑ **Treatment of bradycardia or Bradyarrhythmias**

1- Identification and treatment of the cause, such as removal of causative drugs

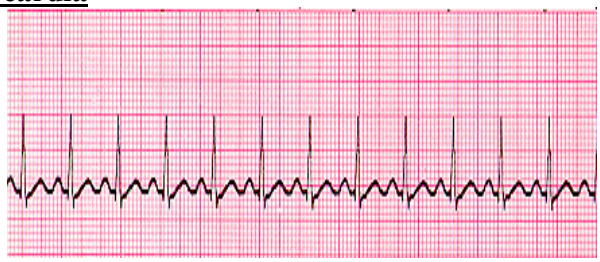
2- Immediate treatment is normally to decrease vagal tone with intravenous atropine, which will: Decrease AV block & Increase the SA rate

- It is important to note that it will take a minute or longer to see initial signs of benefit and at least 5 minutes to observe maximum effect
- Doses of 300-600 µg of atropine may be given up to six times at 1-minute intervals until benefit is observed

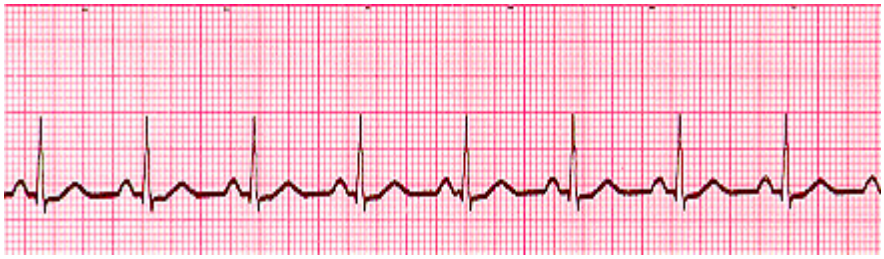
3- If atropine is not effective, intravenous Epinephrine or Isoprenaline may be used to enhance sympathetic tone

II. Tachyarrhythmia

1. **Sinus Tachycardia**



SINUS TACHYCARDIA



Sinus rhythm

- An excessive heart rate or fast pace than normal above 100 beats per minute which originates from the SA node
- Causes include stress, fright, illness as hyperthyroidism and exercise.
- Medications may be required to suppress the rhythm

❋ **ECG**

- Rhythm - Regular
- Rate - More than 100 beats per minute
- QRS Duration - Normal
- P Wave - Visible before each QRS complex
- P-R Interval - Normal

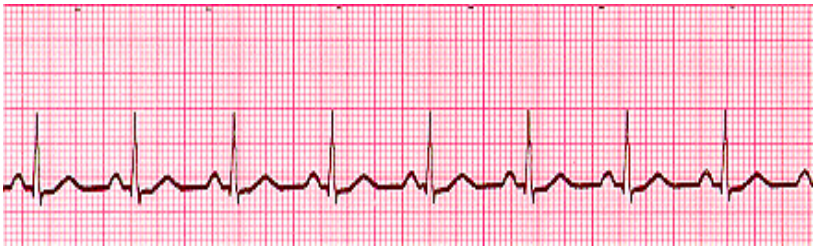
2. Atrial arrhythmia

A. Atrial flutter

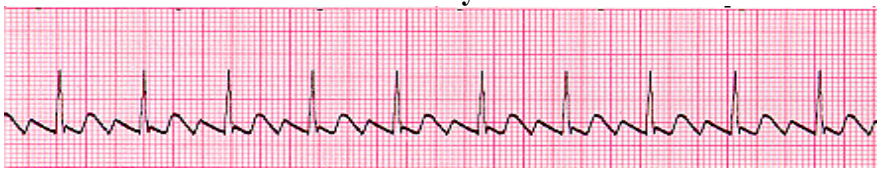
- Atrial flutter denotes a fast, regular rhythm 230-350/minute originating in the atria.
- Rapid regular atrial activation
- Results in regular ventricular response & pulse that is approximately 110-160 beat/min as AV node exerts a protective effect on heart rate by blocking atrial impulses in excess of about half of impulses/minute
- The prominent mechanism of Atrial flutter is reentry tachycardia

B. Atrial fibrillation

- Extremely rapid ,disorganized atrial activation (400-600 beat/min) due to multiple ectopic foci of atrial cells that creates a chaotic movements of impulses
- Most of Supraventricular (atrial) impulses , are not conducting to ventricles the due to protective effect of AV node causing slow ventricular response (120-180 beat/min) with irregular beats or pulses
- Cardiac output is decreased
- Exercise intolerance is common
- The mechanism of Atrial fibrillation is reentry tachycardia.



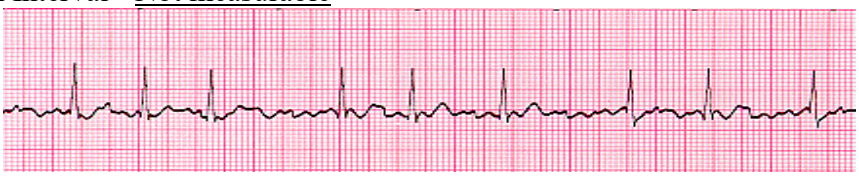
Sinus rhythm



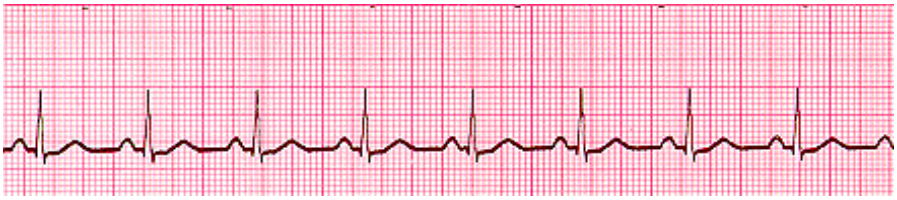
Atrial flutter

❋ **ECG**

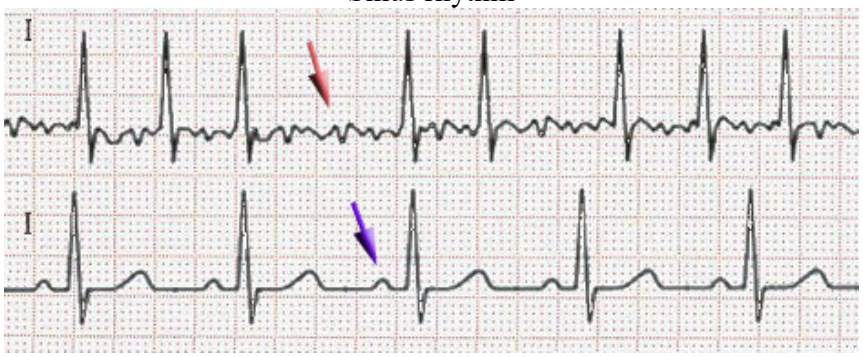
- Rhythm - Regular
- Rate - Around 110 beats per minute
- QRS Duration - Usually normal
- P Wave - Replaced with multiple F (flutter) waves, usually at a ratio of 2:1 (2F - 1QRS) but sometimes 3:1with ,masking T-Wave
- P-R Interval - Not measurable



Atrial fibrillation



Sinus rhythm



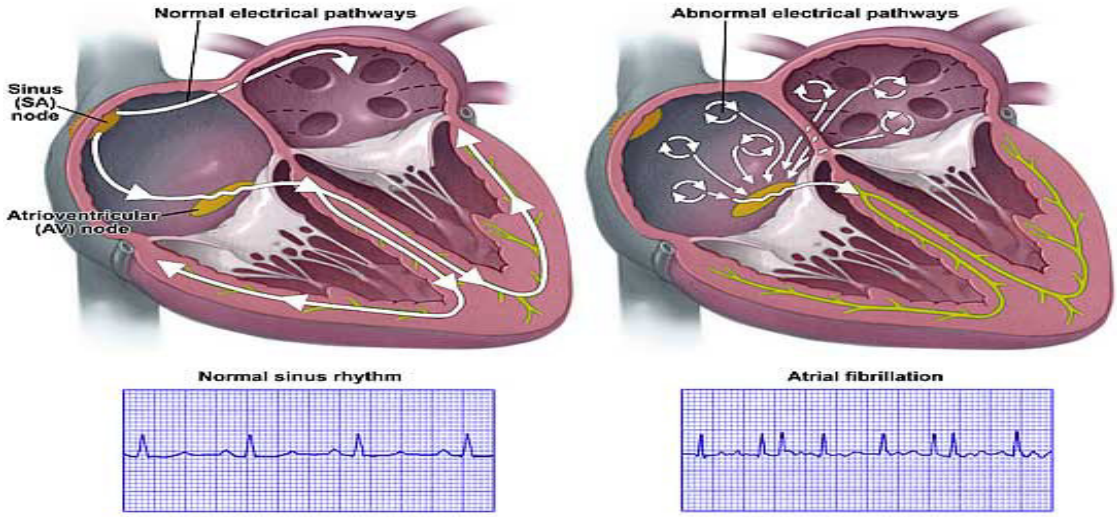
ECG of atrial fibrillation (top) and normal sinus rhythm (bottom).
The purple arrow indicates a P wave, which is lost in atrial fibrillation

- Many sites within the atria are generating their own electrical impulses, leading to irregular conduction of impulses to the ventricles that generate the heartbeat. This irregular rhythm can be felt when palpating a pulse

❋ **ECG**

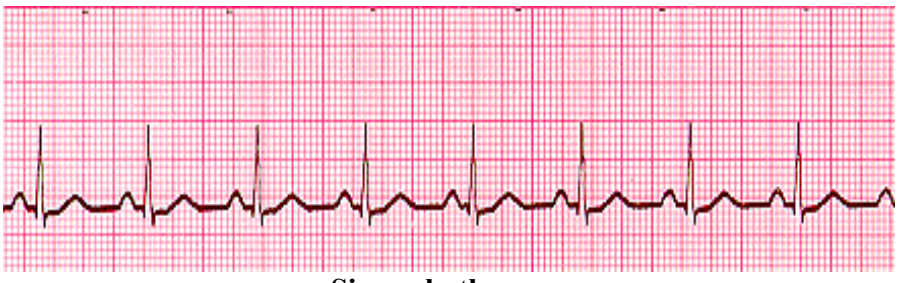
- Rhythm - irregular
- Rate - usually 120-180 beats per minute
- QRS Duration - Usually normal
- P Wave - Not distinguishable or lost
- P-R Interval - Not measurable

- The atria fire electrical impulses in an irregular fashion causing irregular heart rhythm

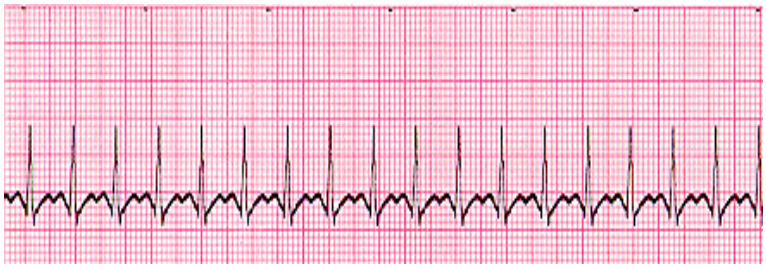


C. Supraventricular tachycardia (SVT)

- It is also called a narrow complex tachycardia
- Supraventricular, have a general meaning such as originating above the ventricles, but can commonly denote something more specific, such as from the AV node
- Impulses stimulating the heart are not being generated by the sinus node, but instead are coming from a collection of tissue around and involving the atrio-ventricular (AV) node
- It is not under direct control from the SA node
- Regular rhythm with fast rate
- Acute Supraventricular tachycardia is a classical example of this arrhythmia



Sinus rhythm



SVT

❋ **ECG**

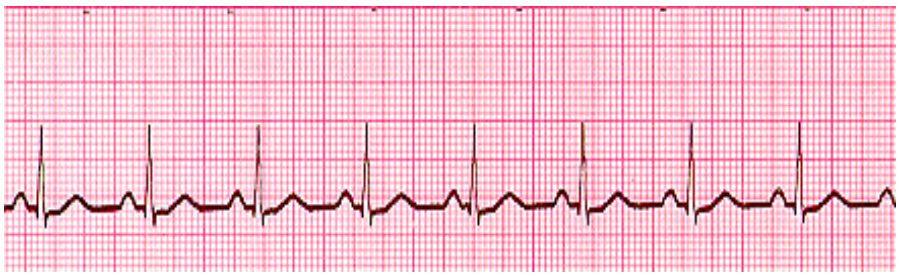
- Rhythm: Regular
- Rate: 140-200 beats per minute i.e. so fast
- QRS Duration: Usually normal but narrow i.e. narrow complex tachycardia
- P Wave: Precedes T wave and close to it
- P-R Interval: Depends on site of Supraventricular pacemaker

D. Ventricular tachycardia

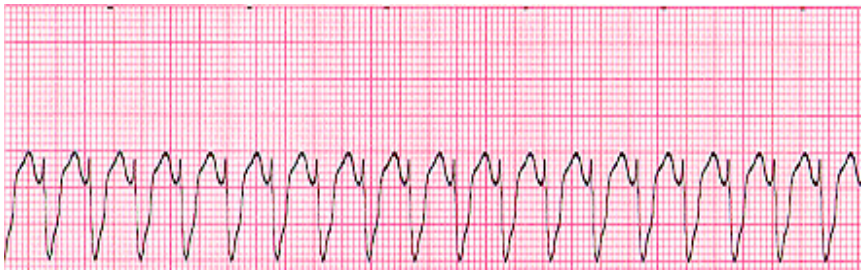
- Ventricular tachycardia is a fast heart rhythm, that originates in one of the ventricle of the heart
- Results from abnormal tissues in the ventricles generating a rapid and regular or irregular heart rhythm according to type
- This is a potentially life-threatening arrhythmia because it may lead to: Ventricular fibrillation, Asystole & Sudden death due to poor COP

a. Acute ventricular tachycardia (AVT)

- It is the most common cause of death in patient with myocardial infarction
- COP is impaired
- May propagate to ventricular fibrillation or cardiac arrest
- Require rapid management



Sinus Tachycardia

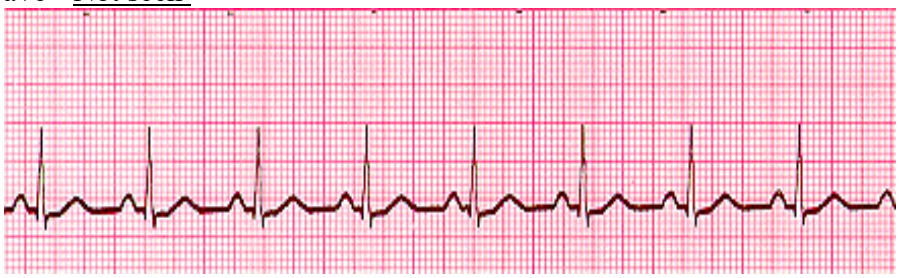


AVT

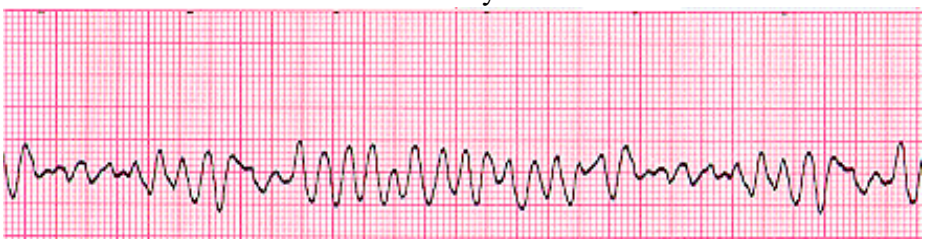
b. Ventricular fibrillation

❋ **ECG**

- Rhythm - Regular
- Rate - 180-190 Beats per minute
- QRS Duration - Prolonged
- P Wave - Not seen



Sinus rhythm



Ventricular Fibrillation (VF)

- Disorganized electrical signals cause the ventricles to quiver instead of contract in arhythmic fashion.
- A patient will be unconscious as blood is not pumped to the brain.
- Immediate treatment by defibrillation is indicated.
- This condition may occur during or after a myocardial infarct.

❋ **ECG :**

- Rhythm - Irregular
- Rate - 300, disorganized
- QRS Duration - Not recognizable
- P Wave - Not seen

❑ **Treatment of arrhythmias**

- Treatment of arrhythmias involves consideration of five "Cs"; causes, coagulation, control, conversion, and cure
- In all cases, physicians will need to look for:

1. **Causes that can be removed**
   - Removal of arrhythmogenic drugs or stimulants such as caffeine, alcohol and smoking
   - investigation of other medical causes, including abnormal thyroid function and abnormal serum electrolyte concentrations is essential.
   - Behavioral modifications to avoid stress and anxiety may help.
2. Consider protecting the patient against stroke with anticoagulant therapy; this is particularly important in atrial fibrillation
3. Control of ventricular rate, to ensure good cardiac output despite an abnormal atrial rhythm
4. Converting the heart to a normal rhythm by means of electricity or drugs
5. Cure of the patient means that the arrhythmia does not return.

❑ **Criteria taken in consideration for treatment of an arrhythmia include:**

1. The arrhythmia causes hemodynamic failure (poor circulation)
2. The patient is distressed by extra or missed beats (palpitations)
3. Tachycardia are known to lead to an increased risk of the development, over months or years, of cardiomyopathy (heart muscle damage) and therefore prolonged tachycardia may be an indication for treatment
4. The aim of treatment is
   - To restore a satisfactory circulation
   - To prevent further episodes of poor circulation or arrhythmia.

❑ Antiarrhythmics

A. Medical cardio-version by antiarrhythmics drugs

❑ **CLASS 1 (membrane stabilizers or sodium channel blocker)**

- Class 1A: Qunidine, Procainamide, Disopyramide
- Class 1B: Mexilitine, Lidocaine, Tocainide
- Class 1C: Flecainide, Propafenone

☒ ***MOA***

- Block sodium channel by slowing phase 0 depolarization in ventricular muscle fibers the Slow conduction velocity and decrease excitability
- Decrease automatic properties of sodium dependent conduction tissue.

❑ ***Clinical uses***

- Automatic tachycardia
- Reentrant tachycardia

❑ **Class 2 : The beta-antagonists**

- Propranolol
- Esmolol
- Metoprolol

☒ ***MOA***: Anti-adrenergic action, so antagonizing increased conduction velocity

❑ **Class 3 (Potassium Channel blockers)**

- Bretylium
- Amiodarone
- Sotalol
- Dofetilide
- Amiodarone may causes hypothyroidism: low T4, elevated TSH, cool skin, decrease HR, obesity

☒ ***MOA***

- Delay phase 3 depolarization or rapid Repolarization ,
- Prolong refractory period.

❑ **Class 4 (Calcium channel blockers)**

- Verapamil and Diltiazem

☒ ***MOA***

- Decrease automaticity of ca- dependent tissue in SA & AV nodes.
- Slow conduction velocity
- Prolong refractory period

❑ **Other antiarrhythmics**

a. **Digoxin**

- Prolong the refractory period
- Diminish conduction velocity in AV node
- its side effects include N,V, tremors and arrhythmia

b. Adenosine

- At high doses it:
    - decreases conduction velocity by temporary block of AV node
    - decreases automaticity in AV node
- IV adenosine is a drug of choice to treat acute supraventricular tachycardia
- It has short duration of action

B. Antithrombotic therapy in arrhythmia : Antithrombotic therapy is indicated in case of:

a. **Atrial fibrillation**

- Atrial fibrillation is associated with a high incidence of stroke

- Nearly all patients with AF should be given oral anticoagulants or, if that is contraindicated, aspirin can be used
- Warfarin, adjusted to give an international normalized ratio (INR) in the range 2-3 to reduces stroke rate by two-thirds in all patient groups, with little risk of excess bleeding
- Dipyridamole and aspirin combination can be used
- Clopidogrel may also be used.

b. Direct current or DC cardioversion

- DC cardioversion may lead to strokes
- So, DC cardioversion for AF is usually preceded by 3 weeks of anticoagulation therapy and followed by 4 weeks of further anticoagulant treatment.

❑ **Dug selection in arrhythmia**

1. Atrial flutter

- Drug of choice is beta blocker as propranolol or verapamil
- Beta blocker is a drug of choice since they decrease heart rate and promote conversion to sinus rhythm
- Beta blocker is a drug of choice for prophylaxis against arrhythmia for patients with myocardial infarction
- Alternative is digoxin

2. Atrial fibrillation

- Drug of choice is beta blocker as propranolol or amiodarone plus anticoagulant therapy
- Long term low doses anticoagulant therapy is required since the risk of stroke is high during atrial fibrillation
- Alternative is dofetilide

3. Acut suravericular tachycardia

- Adenosine is DOC
- Alternative is Verapamil

4. Acute ventricular tachycardia

- Lidocaine or amiodarone is DOC

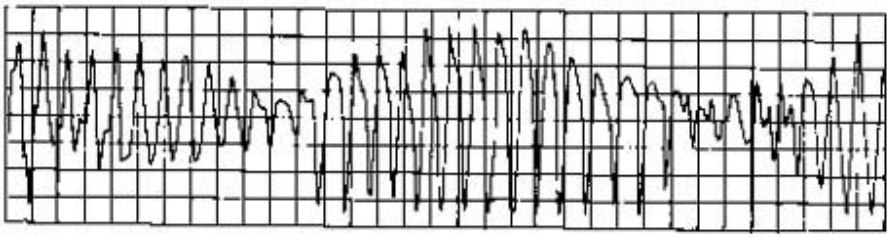
5. Ventricular fibrillation

- Amiodarone is DOC
- Lidocaine is an alternative

⌘ **Hazards or Side effects of antiarrhythmics**

- All antiarrhythmics except class II and class IV are proarrhythemics so they may cause arrhythmia

- they can induce a ventricular arrhythmia called Torsades de pointes, a fast ventricular rhythm or tachycardia (200 beats per min) with polymorphic QRS complexes and a characteristic electrocardiogram (ECG)



Torsade de pointes ventricular tachycardia

- Quindine: it causes cinchonism i.e. headache. Dizziness, tinnitus
- Procainamide and lidocaine : CNS toxicity
- Disopyramide: anticholinergic side effects
- flecainide : N, blurred vision, headache
- Amiodarone: may causes hypothyroidism: low T4, elevated TSH, cool skin, decrease HR, obesity
- Propranolol: bronchospasm?
- Deltiazem and verapamil: negative ionotropic effect? hypotension

C. CARDIOVERSION USING ELECTRICAL CURRENT

1. DC Cardio-version or external defibrillator

- It is used as a treatment for some types of arrhythmia, such as:
  1. Atrial fibrillation 2- Atrial flutter 3. Ventricular tachycardia
- Direct current (DC) cardioversion is an electric shock used to help your heart beat at normal rhythm.
- Electrical (DC) cardioversion is usually given if your arrhythmia has lasted longer than 48 hours.
- DC cardioversion is less likely to work if the arrhythmia has been present for over a year.
- Electrical (DC) cardio-version procedures
- Following sedation or general anaesthesia, a therapeutic dose of electrical energy to the affected heart with a device called a DC cardiovesion or external defibrillator through two pads placed on your chest.
- This electrical energy depolarizes a critical mass of the heart muscle, terminates the arrhythmia, and allows normal sinus rhythm to be reestablished by the body's natural pacemaker, in the SA node of the heart.
- DC cardioversion usually takes 5 to 10 minutes.
- Your heart rate and rhythm is monitored throughout the procedure, and your doctor can see immediately if the procedure has reset your heart to its normal rhythm.

- Side-effects of Electrical (DC) cardioversion
- temporary drop in blood pressure,
- headache, dizziness , flushing and blood coagulation

2. **Implanted Cardioverter Defibrillation or ICD**

- Defibrillation is a common treatment for life-threatening cardiac arrhythmias as ventricular fibrillation
- An implantable cardioverter defibrillator (ICD) is a small device that's placed in your chest.
- The device uses electrical pulses or shocks to help control life-threatening, irregular heartbeats, especially those that could cause sudden cardiac arrest (SCA).
- During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm causing arrhythmias.
- When ventricular arrhythmias occur, the heart can't effectively pump blood. You can pass out within seconds and die within minutes if not treated.
- An ICD has wires with electrodes on the ends that connect to your heart chambers.
- The ICD will continually monitor your heart rhythm.
- If the device detects an irregular rhythm in your ventricles, it will use low-energy electrical pulses to restore a normal rhythm.
- If the low-energy pulses don't restore your normal heart rhythm, or if your ventricles start to quiver rather than contract strongly, the ICD will switch to high-energy electrical pulses for defibrillation.
- These pulses last only a fraction of a second, but they can be painful.

3. **Pacemaker**

- It is used to treat arrhythmias, fainting spells (syncope), congestive heart failure and hypertrophic cardiomyopathy
- A pacemaker is a device that sends small electrical impulses to the heart muscle to maintain a suitable heart rate or to stimulate the lower chambers of the heart (ventricles)
- When your heart rate drops, the pacemaker generates (fires) an impulse that passes through the lead to the heart muscle. This causes the heart muscle to contract, creating a heart beat
- Pacemaker usually only used after the AV node (where the heart's electrical signals pass through) has been destroyed on purpose using ablation.
- An ICD is similar to a pacemaker, but there are some differences.
  1. Pacemakers can only give low-energy electrical pulses
  2. They're often used to treat less dangerous heart rhythms, such as those that occur in the upper chambers of your heart or atrial arrhythmias

❑ **Emergency treatment of arrhythmias in adults**

♣ Acute life-threatening arrhythmias may result in haemodynamic failure and serious acidosis that lead to asystole or cardiac arrest

- ♣ Fast but careful management is required to prevent permanent damage or death
- ♣ The emergency treatment options are:
- Adrenaline (epinephrine), atropine and lidocaine can be in 10 mL of isotonic saline
- **The use <u>lidocaine or bretylium</u> as an adjunct to <u>external electrical defibrillation</u> is common**
- Acidosis may cause widespread problems, including serious arrhythmias, and sodium bicarbonate (50 mmol) may be given to counteract acidosis
- Fast rhythms in which the origin is unclear, and may be ventricular, atrial or nodal, can be analyzed by giving adenosine very rapidly to produce a temporary AV block
- Direct-current cardio-version (DCC) to restore sinus rhythm.

Infective endocarditis

❑ Definition

- **Infective Endocarditis(IE):** Is a microbial infection of the endocardial surface of the heart
- **Common site:** heart valve, but may occur at septal defect, on chordae tendinae or in the mural endocardium

❑ Classification:

- Acute or subacute-chronic on temporal basis, severity of presentation and progression
- By organism
- Native valve or prosthetic valve

▪ Acute

- Toxic presentation
- Progressive valve destruction & metastatic infection developing in days to weeks
- Most commonly caused by S. aureus

▪ Subacute

- Mild toxicity
- Presentation over weeks to months
- Rarely leads to metastatic infection
- Most commonly S. viridans or enterococcus

❑ PATHOGENESIS

▪ Characteristic pathological lesion:

♣ **The vegetation**

- Variable in size
- Amorphous mass of fibrin & platelets
- Abundant organisms
- Few inflammatory cells

▪ Altered valve surface

- Animal experiments suggest that IE is almost impossible to establish unless the valve surface is damaged

▪ **Deposition of platelets and fibrin** – nonbacterial thrombotic vegetation (NBTE)

▪ **Bacteraemia** attaches to platelet-fibrin deposits

- Covered by more fibrin
- Protected from neutrophils
- Division of bacteria
- Mature vegetation

Haemodynamic Factors

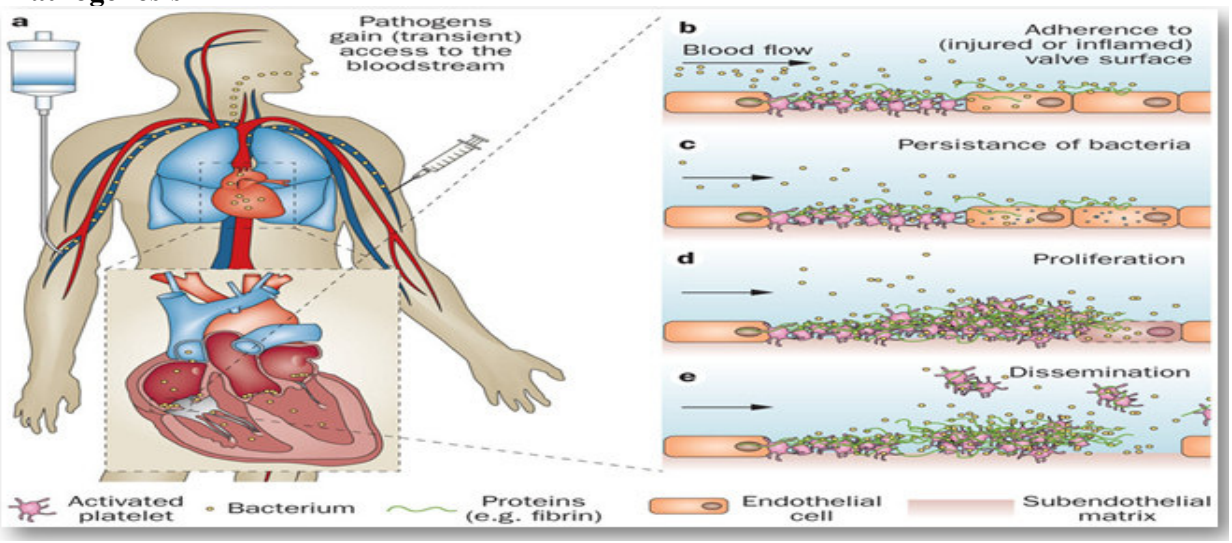
- Bacterial colonisation more likely to occur around lesions with high degrees of turbulence eg. small VSD, valvular stenosis.
- Large surface areas, low flow and low turbulence are less likely to cause IE e.g large VSD.

Bacteraemia

♣ Transient bacteraemia occurs when a heavily colonised mucosal surface is traumatized.

- Dental extraction
- Periodontal surgery
- Tooth brushing
- Tonsillectomy
- Operations involving the respiratory, GI or GU tract mucosa
- Oesophageal dilatation
- Biliary tract surgery

❑ Pathogenesis



❑ <u>Site of Infection</u>

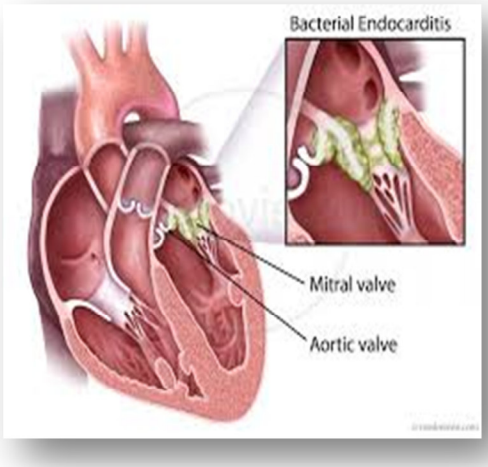
Aortic valve more common than Mitral

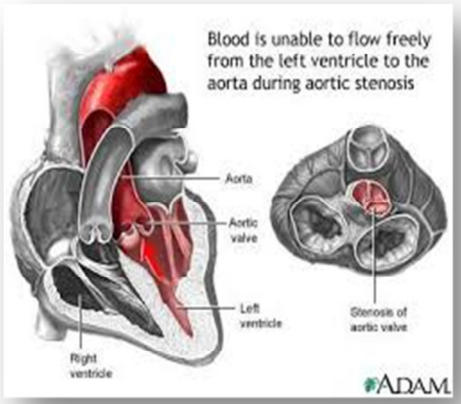
➢ Aortic:

- Vegetation usually on ventricular aspect, all 3 cusps usually affected
- Perforation or dysfunction of valve
- Root abscess

➢ Mitral:

- Dysfunction by rupture of chordae tendinae





❑ Epidemiology

- Case rate may vary between 2-3 cases /100,000 to as high as 15-30/100,000 depending on incidence of i.v. drug abuse and age of the population
- 55-75% of patients with native valve endocarditis (NVE) have underlying valve abnormalities:
  - MVP (mitral valve prolapse)
  - Rheumatic
  - Congenital
  - i.v. drug abuse
- Incidence in intravenous drug abusers (IVDA) group is estimated at 2000 per 100,000 person-years, even higher if there is known valvular heart disease
- Increased ageing leads to more degenerative valvular disease, placement of prosthetic valves and increased exposure to nosocomial bacteremia.

❑ PROSTHETIC VALVES

- 7-25% of cases of infective endocarditis
- The rates of infection are the same at 5 years for both mechanical and bioprostheses, but higher for mechanical in first 3 months
- Culmulative risk: 3.1% at 12 months and 5.7% at 60 months post surgery

✠ Onset:

- within 2 months of surgery: early onset and usually hospital acquired
- 12 months post surgery: late onset and usually community acquired.

❑ Nosocomial Infective Endocarditis

- 7-29% of all cases seen in tertiary referral hospitals
- At least half linked to intravascular devices
- Other sources GU and GIT procedures or surgical-wound infection

Aetiological Agents

I. Streptococci
   - Viridans streptococci/α-haemolytic streptococci
   - S. mitis, S. sanguis, S. oralis
   - S. bovis: Associated with colonic carcinoma

II. Enterococci
   - E. faecalis, E. faecium
   - Associated with GU/GI tract procedures
   - Approx. 10% of patients with enterococcal bacteraemia develop endocarditis

III. Staphylococci
   - Staphylococcci have surpassed viridans streptococci as the most common cause of infective endocarditis
   - Coagulase-Positive (S. aureus): Native valves / acute endocarditis
   - Coagulase-Negative (Staph. Epi): Prosthetic valve endocarditis

IV. Gram-negative rods
   - HACEK group: Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella
   - E. coli, Klebsiella etc: Uncommon
   - Pseudomonas aeruginosa: IVDA
   - Neisseria gonorrhoae(Rare since introduction of penicillin)

V. Others
   - Fungi: Candida species, Aspergillus species
   - Q fever
   - Chlamydia
   - Bartonella
   - Legionella

RISK FACTORS

1. Structural heart disease
2. Rheumatic, congenital.
3. Prosthetic heart valves
4. Injected drug use
5. Invasive procedures e.g Intracardiac pacemaker
6. Other infection with bacteremia (e.g. pneumonia, meningitis)
7. Immune compromised states
8. History of infective endocarditis

DIAGNOSIS

CLINICAL PICTURE

- Fever, most common symptom, sign (but may be absent)
- Anorexia, weight-loss, malaise, night sweats
- Heart murmur
- Petechiae on the skin, conjunctivae, oral mucosa
- Splenomegaly
- **Right-sided endocarditis** is not associated with peripheral emboli/phenomena but pulmonary findings predominate
- **Oslers' nodes**
- Tender, s/c nodules
- **Janeway lesions**
- Non-tender erythematous, haemorrhagic, or pustular lesions often on palms or soles.

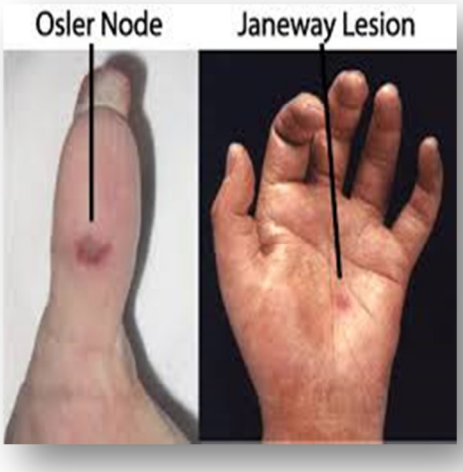
Prosthetic valve-Presentation

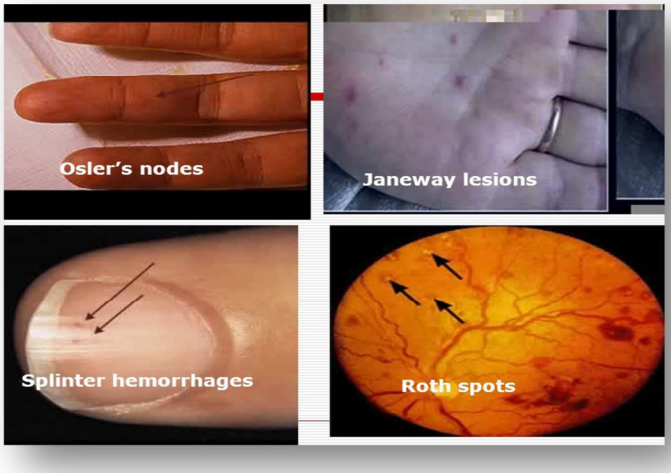
- Often indolent illness with low grade fever or acute toxic illness
- Locally invasive : new murmurs and congestive cardiac failure
- If prosthetic valve in situ and unexplained fever suspect endocarditis

Nosocomial Endocarditis

- May present acutely without signs of endocarditis
- Suggested by: Bacteremia persisting for days before treatment or for 72 hours or more after the removal of an infected catheter and initiation of treatment (esp in those with abnormal or prosthetic valves)

- Risk if prosthetic valve and bacteremia: 11%
- Risk if prosthetic valve and candidaemia: 16%





COMPLICATIONS

☒ Cardiac :

- congestive cardiac failure (infection beyond valve)
- valvular damage, more common with aortic valve endocarditis
- Systemic emboli
- Risk depends on
- Valve (mitral>aortic)
- Size of vegetation, (high risk if >10 mm)
- 20-40% of patients with endocarditis
- risk decreases once appropriate antimicrobial therapy started.

☒ **Prolonged Fever:**

- usually fever associated with endocarditis resolves in 2-3 days after appropriate antimicrobial therapy with less virulent organisms and 90% by the end ot the second week.

☒ **Recurrent fever:**

- infection beyond the valve
- focal metastatic disease
- drug hypersensitivity
- nosocomial infection or others e.g. Pulmonary embolus

Investigations

1) Blood culture
2) Echo
   - TTE
   - TOE
3) CBC/ESR/CRP
4) Rheumatoid Factor

Duke Criteria

☒ **Definite**

- 2 major criteria
- 1 major and 3 minor criteria
- 5 minor criteria
- pathology/histology findings

☒ **Possible**

- 1 major and 1 minor criteria
- 3 minor criteria

☒ **Rejected:**

- firm alternate diagnosis
- resolution of manifestations of IE with 4 days antimicrobial therapy or less

Major Criteria

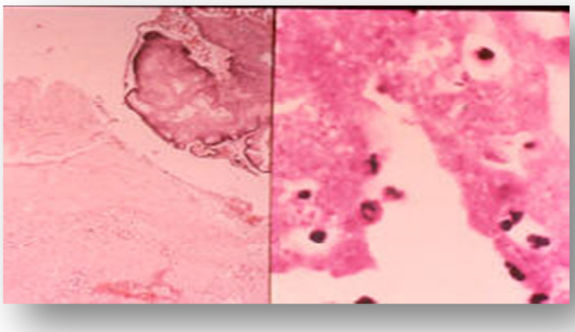
➢ Positive blood culture

- Typical organism from two cultures
- Persistent positive blood cultures taken > 12 hours apart
- Three or more positive cultures taken over more than 1 hour.

➢ Endocardial involvement

- Positive echocardiographic findings of vegetations

Histological evidence



❋ **Minor Criteria**

- Predisposition: Predisposing valvular or cardiac abnormality
- Intravenous drug misuse
- Pyrexia ≥38°C
- Embolic phenomenon
- Vasculitic/ immunologic phenomenon
- Blood cultures suggestive:- organism grown but not achieving major criteria
- Suggestive echocardiographic findings

❋ **Blood cultures**

- Key diagnostic investigation in infective endocarditis.
- Isolation of microorganism from culture is important for diagnosis and also for treatment.
- At least 3 sets of samples should be taken from different venepuncture sites over 24 hours.

❋ **Serology**

- Can be sent when the diagnosis is suspected and the cultures are negative.
- They aid in cases where the organisms will not grow in blood cultures (Coxiella, Legionella, Bartonella)

❋ **ECG**

- To detect complications like MI, conduction abnormalities.

❋ **CHEST X RAY**

❋ **ECHO**

- Trans Thoracic Echocardiograpy (TTE)
  - rapid, non-invasive – excellent specificity (98%) but poor sensitivity.
- Transesophageal Echo (TOE)
  - more invasive, sensitivity up to 95%, useful for prosthetic valves and to evaluate myocardial invasion
  - Negative predictive valve of 92%
  - TOE more cost effective in those with S. aureus catheter-associated bacteremia and bacteremia/fever and recent IVDA

❑ **Culture Negative Endocarditis**

- 5-7% of patients with endocarditis will have sterile blood cultures
- Fasidious or non-culturable organism
- Non-infective endocarditis
- Withhold empirical therapy until cultures drawn

❑ **TREATMENT**

☒ Goal of Therapy
- Eradicate infection
- Definitively treat sequelae of destructive intra-cardiac and extra-cardiac lesions

☒ Antibiotic Therapy
- Treatment tailored to etiologic agent
- Important to note MIC/MBC relationship for each causative organism and the antibiotic used
- High serum concentration necessary to penetrate avascular vegetation
- Empirical therapy should be started as soon as possible targeting most likely pathogens
- Start Treatment before blood cultures turn positive when:
  - Suspected ABE
  - Hemodynamic instability
- Fever should disappear with 7 – 10 days antimicrobial efficient treatment
- Antimicrobial therapy
  - Use a bactericidal regimen
  - Use a recommended regimen for the organism isolated
  - Repeat blood cultures until blood is demonstrated to be sterile

☒ Surgery: Get cardiothoracic teams involved early

✵ **<u>Antibotic regimen for infective endocarditis</u>**

➢ **Streptococci**
- Benzyl penicillin (1.2g 4 hourly) 4-6 weeks
- Gentamicin (1mg/kg 8-12 hourly) 4-6 weeks

➢ **Enterococci**
- *Ampicillin sensitive*
  - Ampicillin (2 g 4 hourly) 4-6 weeks, and
  - Gentamicin (1mg/kg 8-12 hourly)
- *Ampicillin resistant*
  - Vancomycin(1g 12hourly) 4-6 weeks, and
  - Gentamicin (1mg/kg 8-12 hourly)

➢ **Staphycocci**
- *Penicillin sensitive*
  - Benzyl penicillin I.V(1.2 g 4 hourly)

- *Penicillin resistant but methicillin sensitive*
  - Flucloxacillin I.V (2g 4 hourly)
- *Both penicillin and methicillin resistant*
- Vancomycin I.V (1g 12 hourly) and Gentamicin

➢ Staphylococci

a. Native valve
   - Flucloxacillin +/- aminoglycoside
   - Vancomycin +/- aminoglycoside/ rifampicin

b. Prosthetic valve
   - Flucloxacillin + aminoglycoside + rifampicin
   - Vancomycin + aminoglycoside + rifampicin

❑ **Surgical Therapy:**

❋ **Indications:**

1. Congestive cardiac failure
2. perivalvular invasive disease
3. uncontrolled infection despite maximal antimicrobial therapy
4. Pseudomonas aeruginosa, Brucella species, Coxiella burnetti, Candida and fungi.
5. Presence of prosthetic valve endocarditis unless late infection
6. Large vegetation
7. Major embolus
8. Heart block

❑ **Prevention**

1. Antimicrobial prophylaxis is given to at risk patients when bacteraemia-inducing procedures are performed
2. Prior endocarditis
3. Unrepaired cyanotic congenital heart diseases
4. Completely repaired congenital heart disease in their first 6 months
5. Prosthetic heart valves
6. Incompletely repaired congenital heart diseases
7. Cardiac transplant valvulopathy

➢ Following are the antibiotic regimens recommended by the American Heart Association for antibiotic prophylaxis:

- Oral Amoxicillin 1 hour before the procedure
- Intravenous or intramuscular ampicillin 1 hour before the procedure
- In patients allergic to penicillins:
  - Azithromycin or clarithromycin orally 1 hour before the procedure
  - Cephalexin orally 1 hour before the procedure
  - Clindamycin orally 1 hour before the procedure

Hypovolemic Shock

Definition:

- Reduction in intravascular volume leading to insufficient oxygen delivery to cell (mitochondria)
- Shock occurs when a diminished amount of blood is available to the circulatory system.
- The vascular system fails to hold the fluid portion of the blood.
- Vasodilation of the blood vessels occurs and disrupts the osmotic fluid balance in the body. Plasma cells leave the blood and enter the interstitial spaces the formed elements remain in the blood, Blood viscosity increases, the rate of blood flow decreases insufficient amounts of O2 are being transported in the blood

- Hypovolemic shock is an emergency condition in which severe blood and fluid loss make the heart unable to pump enough blood to the body due to decreased preload.
- The diminished preload decreases the CO and the SVR increases in an effort to compensate for the diminished CO and maintain perfusion to the vital organs.
- It leads to multiple organs failure.

Predisposing Factors

- Extreme fatigue
- Extreme exposure to heat or cold
- Extreme dehydration
- Illness
- Severe injury
- Revealed hemorrhage(External)
- Penetrating trauma, open arterial wound
- Concealed hemorrhage (Internal)
- Intera -abdominal bleeding, aortic aneurysm
- Burns
- Sever vomiting & diarrhea
- Excessive diuresis

Signs and Symptoms

- Low Blood Pressure
- Systolic BP is usually below 90 mmHg
- Diastolic BP is usually below 60 mmHg
- Pulse is rapid and weak
- Respiration is rapid and shallow
- Skin is pale, cool, and clammy
- Drowsiness

	Class I	Class II	Class III	Class IV
Absolute blood loss	<750mL	750-1500mL	1500-2000mL	>2000mL
Relative blood loss	<15%	15-30%	30-40%	>40%
Pulse rate	<100	100-120	120-140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal/increased	Decreased	Decreased	Decreased
Capillary refill	Normal	Decreased	Decreased	Decreased
Respiratory rate	14-20	20-30	30-40	>35
Urine output (mL/h)	>30	20-30	5-15	Negligible
CNS-Mental status	Slightly anxious	Anxious	Anxious confused	Confused lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood
Modified from: Committee on Trauma of the American College of Surgeons. Advanced Trauma Life Support (ATLS).				

Hypovolemic Shock

- Results from trauma in which there is blood loss decreased blood volume causes a decrease in blood pressure insufficient amounts of O2 is being transported to body tissues and organs
- Results when the lungs are unable to supply enough O_2 the circulating blood
- Trauma that may produce respiratory shock include:
- Pneumothorax
- Injury to the respiratory control center
- Results when the lungs are unable to supply enough O_2 the circulating blood
- Trauma that may produce respiratory shock include:
- Pneumothorax
- Injury to the respiratory control center

What acid/base category would be expected?

- The effect of fluid loss on acid-base balance is variable.
- Although many patients maintain a normal extracellular pH, either metabolic acidosis or metabolic alkalosis can occur.
- Lactate acidosis is common in cases of hypovolemic shock.
- **Lactic acidosis,** considered a type of metabolic acidosis, is a physiological condition characterized by low pH in body tissues and blood (acidosis) accompanied by the buildup of lactate.
- Lactic acidosis is characterized by lactate levels >5 mmol/L and serum pH <7.35.
- **Type A lactic acidosis** is the most common type of lactic acidosis in hypovolemic shock.

What is the effect of this kind of shock on kidneys, heart, lungs, brain, and intestines?

♣ **Kidneys**

- The urine output will decrease do to renal hypo perfusion.
- Blood loss 750-1500ml (Urinary output mildly affected)
- **Blood loss 1500-2000** (Urinary output mildly/severely affected.)
- **Blood loss >2000** (Severe oliguria or anuria).

♣ **Heart**

- Cardiovascular signs are due to **adrenergic response** to blood loss.

(Shock class I)	(Shock class II)	(Shock class III)	(Shock class IIII)
NONE	Tachycardia due to catecholamine release. Weak pulse or absent pulses (they are more significant than weak pulses). Skin: pale, moist and cool.	Tachycardia Hypotension	Tachycardia, very weak pulse. Capillary refill is undetectable. The skin is pale and moist. Blood pressure very low or undetectable.

♣ **Lungs**

- Tachypnea due to central nervous system chemoreceptor stimulation by a decreased pH and hypoxia.

♣ **Brain**

- Symptoms are duo to cerebral hypoper fusion and acidosis.

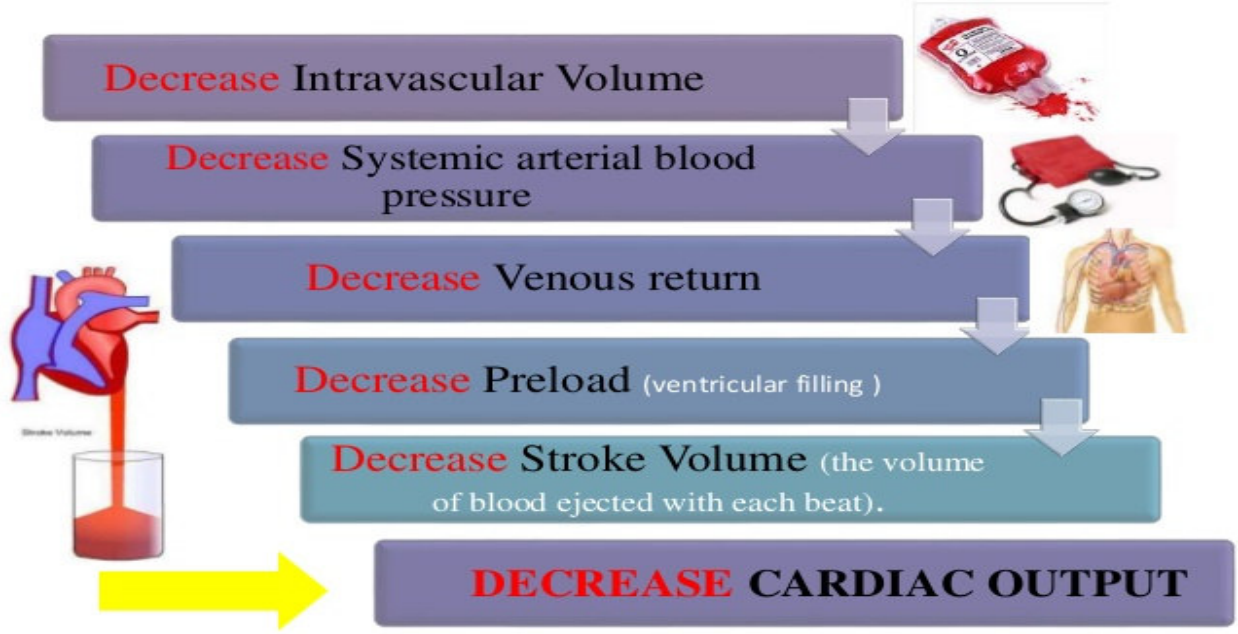
(Shock class I)	(Shock class II)	(Shock class III)	(Shock class IIII)
None or orthostatic dizziness.	Restlessness, anxiety, agitation.	Anxiety, confusion.	Confusion, drowsiness, and coma

♣ **Intestine**

- Decreased intestinal motility due to intestinal hypo perfusion.
- This leads to bilious aspirate “Green liquid in Nasogastric tube aspirate”

❑ **What would be the cardiac output.**

- Hypovolemic shock is characterized by a loss in intravascular volume that results in decreased preload.
- Since preload is one of the determinants of stroke volume, **cardiac output falls.**
- The initial hemodynamic abnormality of fluid loss activates the compensatory mechanisms under neuroendocrine control, which maintain adequate central
- Perfusion despite the fall in cardiac output.
- However, systemic vasoconstriction may lead to tissue ischemia, hypoxia, and eventually to altered cellular function and global organ dysfunction.



❑ **Hypovolemic Shock**

- Reduced intravascular volume?
- No oxygen delivery!
- No aerobic metabolism!

Then…

- Metabolic acidosis (lactic acid production)
- Endoplasmic reticulum swelling
- Mitochondrial damage
- Cell Death!

❑ **Vascular compartments:**

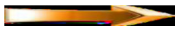
- TBW (60% of IBW)
- Total Body Water
- ICW (40%) ECW (20%)
- Intracellular Water Extracellular Water
- Interstitial Plasma (1/3) (2/3)
- Loss of circulating blood volume (Plasma)
- Normal Blood Volume:
- 7% IBW in adults
- 9% IBW in kids
- Hypovolemic Shock
- Tension
- Pneumothorax
- ~ Impairment of ventricular filling.

❑ **Hemorrhagic shock (3 categories)**

❋ **Compensated:**

- 0-20% of blood loss
- Blood pressure is maintained via increased
- Vascular tone and increased blood flow to vital organs

The body's response:

- Compensated shock  Baroreceptor mediated vasoconstriction!
- Increased epinephrine, vasopressin, angiotensin

➢ **Results in:**

- Tachycardia
- Tachypnea
- Lowered pulse pressure
- Slightly lowered urine output

The Organs who win:

- Brain
- Heart
- Kidneys
- Liver

The Organs who lose:

- Skin
- GI tract
- Skeletal Muscle
- But why the body will make whatever adjustments it can to
- Maintain….Adequate Cardiac Output
- Brain and heart perfusions remain **near normal** while other less critical organ systems are, in proportion to the blood volume deficit, stressed by ischemia.

❋ **Uncompensated:**

- 20-40% loss of blood volume
- Decrease in BP
- Tachycardia

The body's response

- The intravascular volume deficit exceeds the capacity of vasoconstrictive mechanisms to maintain systemic perfusion pressure.
- Increased cardiac output
- Increased respiration
- Sodium retention

Lethal exsanguination:

- 4o %loss of blood volume
- Profound hypotension and
- Inability to perfuse vital organs

The body's response

Lethal exsanguination:

–Obtunded
–Severe hypotension
–Severe tachycardia
–Cold, Clammy
– Death

Caveats

- Athletes
- Pregnancy
- Extremes of age
- Medications
- Hematocrit/Hemoglobin

Management:

- ABCs of trauma (AIRWAY is always first (!Control hemorrhage (splint the limb (!!)
- Obtain IV access and resuscitate with fluids and blood
- 2- liters crystalloid for adults
- cc/kg crystalloid x 2 for kids
- Blood vs. Crystalloid??
- Long term critical care management

Your management goals AFTER securing the

- ABCs:
- Stop the bleeding!
- Restore volume!
- Correct any electrolyte/acid-base disturbances!

- **Volume Resuscitation ~ what are my goals?**
  - **Rapid Responder**
    - Give 500cc-1 Liter crystalloid → rapid Improvement of BP/HR/Urine output
    - < 20% blood loss
    - Surgery consult
- **Volume Resuscitation ~ What are my goals?**
  - **Transient Responder**
    - Give 500cc-1 Liter crystalloid → Improves briefly then deteriorates
    - 20-40% blood loss
    - Continue crystalloid infusion +/- Blood
    - Surgery consult
  - **Non Responder**
    - Give 2 Liters crystalloid/ 2 units Blood → no response
    - > 40% blood loss
    - STAT Surgery consults!
- **Is my volume resuscitation adequate/inadequate?**

- Urine output
- Vital signs
- Skin perfusion
- Pulse Oximetry
- Acidemia??

Anemia

DEFINITION: Anemias are a group of diseases characterized by a decrease in hemoglobin (Hb) or red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood

PATHOPHYSIOLOGY:

- Anemia can be classified on the basis of RBC morphology, etiology, or pathophysiology.

- **Morphologic classifications** are based on cell size. Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B12 or foliate. Microcytic cells are smaller than normal and are associated with iron deficiency whereas normocytic anemia may be associated with recent blood loss or chronic disease.
- Iron-deficiency anemia can be caused by inadequate dietary intake, inadequate GI absorption, increased iron demand (e.g., pregnancy), blood loss and chronic diseases)
- Vitamin B12- and foliate-deficiency anemia can be caused by inadequate dietary intake, absorption, and inadequate utilization. Deficiency of intrinsic factor can cause decrease absorption of vitamin B12 (i.e., pernicious anemia). Foliate-deficiency anemia can be caused by hyper utilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt. Drugs can cause anemia by reducing absorption of foliate (e.g., phenytoin) or by Interfering with corresponding metabolic pathways (e.g., methotrexate).
- Anemia of chronic disease is a hypo proliferative anemia associated with chronic infectious or inflammatory processes, tissue injury, or conditions that release proinflammatory cytokines. The pathogenesis is based on shortened RBC survival, impaired marrow response, and disturbance of iron metabolism. For information on anemia of chronic kidney disease
- In anemia of critical illness, the mechanism for RBC replenishment and homeostasis is altered by, for example, blood loss or cytokines, which can blunt the erythropoietic response and inhibit RBC production.
- Age-related reductions in bone marrow reserve can render the elderly patient more susceptible to anemia that is caused by multiple minor and often unrecognized diseases (e.g., nutritional deficiencies) that negatively affect erythropoiesis. Anemia in children is often due to a primary hematologic abnormality. The risk of iron-deficiency anemia is increased by rapid growth spurts and dietary deficiency.
- Hemolytic anemia results from decreased RBC survival time due to destruction in the spleen or circulation. The most common etiologies are RBC membrane defects (e.g., hereditary spherocytosis), altered Hb solubility or stability (e.g., sickle cell anemia), and changes in intracellular metabolism (e.g., glucose-6-phosphate dehydrogenase deficiency). Some drugs cause direct oxidative damage to RBCs.

CLINICAL PRESENTATION

- Signs and symptoms depend on the rate of development and the age and cardiovascular status of the patient. Acute-onset anemia is characterized by cardiorespiratory symptoms such as tachycardia, lightheadedness, and breathlessness. Chronic anemia is characterized by weakness, fatigue, headache, vertigo, faintness, cold sensitivity, pallor, and loss of skin tone.
- Iron-deficiency anemia is characterized by glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice). These symptoms are not usually seen until the Hb concentration is less than 9 g/dL.
- Vitamin B12 and folate-deficiency anemias are characterized by pallor, icterus, and gastric mucosal atrophy. Vitamin B12 anemia is distinguished by neuropsychiatric abnormalities (e.g., numbness, paresthesias, irritability), which are absent in patients with folate-deficiency anemia.

DIAGNOSIS

- Rapid diagnosis is essential because anemia is often a sign of underlying pathology.
- Initial evaluation of anemia involves a complete blood cell count, reticulocyte index, and examination of the stool for occult blood. Normal Hematologic Values in the following table.

	Reference Range (years)			
Test	***2–6***	***6–12***	***12–18***	***18–49***
Hemoglobin (g/dL)	11.5–15.5	11.5–15.5	M 13.0–16.0 F 12.0–16.0	M 13.5–17.5 F 12.0–16.0
Hematocrit (%)	34–40	35–45	M 37–49 F 36–46	M 41–53 F 36–46
MCV (fL)	75–87	77–95	M 78–98 F 78–102	80–100
MCHC (%)	–	31–37	31–37	31–37
MCH (pg)	24–30	25–33	25–35	26–34
RBC (million/mm^3)	3.9–5.3	4.0–5.2	M 4.5–5.3	M 4.5–5.9
Reticulocyte count, absolute (%)				0.5–1.5
Serum iron (mcg/dL)		50–120	50–120	M 50–160 F 40–150
TIBC (mcg/dL)	250–400	250–400	250–400	250–400
RDW (%)				11–16
Ferritin (ng/mL)	7–140	7–140	7–140	M 15–200 F 12–150
Folate (ng/mL)				1.8–16.0[a]
Vitamin B_{12} (pg/mL)				100–900[a]
Erythropoietin (milliunits/mL)				0–19

F, female; M, male; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution; TIBC, total iron-binding capacity.
[a]Varies by assay method.

- Red blood cell distribution width is a measure of the range of variation of red blood cell (RDW)
- Laboratory findings of anemia of critical illness disease are similar to those of anemia of chronic disease.
- Elderly patients with symptoms of anemia should undergo a complete blood cell count with peripheral smear and reticulocyte count, and other laboratory studies as needed to determine the etiology of anemia.
- Diagnosis of anemia in pediatric populations requires the use of age- and sex-adjusted norms for laboratory values.
- Hemolytic anemia tend to be normocytic and normochromic and to have increased levels of reticulocytes, lactic dehydrogenase, and indirect bilirubin.

DESIRED OUTCOME

- The ultimate goals of treatment in the anemic patient are to alleviate signs and symptoms, correct the underlying etiology (e.g., restore substrates needed for RBC production), and prevent recurrence of anemia.

TREATMENT

IRON-DEFICIENCY ANEMIA

- **Oral iron** therapy with soluble ferrous iron salts, which are not enteric coated and not slow- or sustained-release, is recommended at a daily dosage of 200 mg elemental iron in two or three divided doses (Table -3).
- Diet plays a significant role because iron is poorly absorbed from vegetables, grain products, dairy products, and eggs; iron is best absorbed from meat, fish, and poultry. Administration of iron therapy with a meal decreases absorption by more than 50% but may be needed to improve tolerability.
- **Parenteral iron** may be required for patients with iron malabsorption, intolerance of oral iron therapy, or noncompliance.
- The parental administration, however, does not hasten the onset of hematologic response. The replacement dose depends on etiology of anemia and Hb concentration
- Available parenteral iron preparations have similar efficacy but different pharmacologic, pharmacokinetic, and safety profiles. The newer products, sodium ferric gluconate and iron sucrose, appear to be better tolerated than iron dextran

Salt	Elemental Iron (%)	Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 18 mg iron/5 mL syrup 44 mg iron/5 mL elixir 15 mg iron/0.6 mL drop
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 60 mg/187 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	36 mg/325 mg tablet 27 mg/240 mg tablet
Ferrous fumarate	33	33 mg/100 mg tablet 63–66 mg/200 mg tablet 106 mg/324–325 mg tablet 15 mg/0.6 mL drop 33 mg/5 mL suspension
Polysaccharide iron complex	100	150 mg capsule 50 mg tablet 100 mg/5 mL elixir
Carbonyl iron	100	50 mg caplet

In patients with iron-deficiency anemia:

Adults + children over 15 kg

Dose (mL) = 0.0442 (desired Hb – observed Hb) × LBW + (0.26 × LBW)

LBW males = 50 kg + (2.3 × inches over 5 ft)

LBW females = 45.5 kg + (2.3 × inches over 5 ft)

Children 5–15 kg

Dose (mL) = 0.0442 (desired Hb – observed Hb) × W + (0.26 × W)

In patients with anemia secondary to blood loss (hemorrhagic diathesis or long-term dialysis):

mg of iron = blood loss × hematocrit

where blood loss is in milliliters and hematocrit is expressed as a decimal fraction.

Hb, hemoglobin; LBW, lean body weight; W, weight.

❋ VITAMIN B 12-DEFICIENCY ANEMIA

- Oral vitamin B 12 supplementation appears to be as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B 12 absorption pathways is independent of intrinsic factor. Oral cobalamin is initiated at 1 to 2 mg daily for 1 to 2 weeks, followed by 1 mg daily.
- Parenteral therapy is more rapid acting than oral therapy and should be used if neurologic symptoms are present. A popular regimen is cyanocobalamin 1,000 mcg daily for 1 week, then weekly for 1 month, and then monthly. When symptoms resolve, daily oral administration can be initiated.
- Adverse events are rare with vitamin B 12 therapy.

❋ FOLATE-DEFICIENCY ANEMIA

- Oral foliate 1 mg daily for 4 months is usually sufficient for treatment of folate-deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, the daily dose should be increased to 5 mg.

❋ ANEMIA OF CHRONIC DISEASE

- Treatment of anemia of chronic disease is less specific than that of other anemias and should focus on correcting reversible causes. Iron therapy is not effective when inflammation is present. RBC transfusions are effective but should be limited to episodes of inadequate oxygen transport and Hb of 8 to 10 g/dL.
- Epoetin alfa can be considered, especially if cardiovascular status is compromised, but the response can be impaired in patients with anemia of chronic disease (off-label use). The initial dosage is 50 to 100 units/kg three times weekly. If Hb does not increase after 6 to 8 weeks, the dosage can be increased to 150 units/kg three times weekly.
- Epoetin alfa is usually well tolerated. The hypertension seen in patients with end-stage kidney disease is less common in patients with acquired immune deficiency syndrome.

❋ OTHER TYPES OF ANEMIAS

- Patients with other types of anemias require appropriate supplementation depending on the etiology of anemia.
- In patients with anemia of critical illness, parenteral iron is often utilized but is associated with a theoretical risk of infection. Routine use of epoetin alfa or RBC transfusions is not supported by clinical studies.
- Anemia of prematurity is usually treated with RBC transfusions. The use of epoetin alfa is controversial.
- In the pediatric population, the daily dose of elemental iron, administered as iron sulfate, is 3 mg/kg for infants and 6 mg/kg for older children for 4 weeks. If response is seen, iron should be continued for 2 to 3 months to replace storage iron pools. The dose and schedule of vitamin B12 should be titrated according to clinical and laboratory response. The daily dose of folate is 1 to 3 mg.
- Treatment of hemolytic anemia should focus on correcting the underlying cause. There is no specific therapy for glucose-6-phosphate dehydrogenase deficiency, so treatment consists of avoiding oxidant medications and chemicals. Steroids, other immune suppressants, and even splenectomy can be indicated to reduce RBC destruction.

EVALUATION OF THERAPEUTIC OUTCOMES

- In iron-deficiency anemia, iron therapy should cause reticulocytosis in 5 to 7 days and raise Hb by 2 to 4 g/dL every 3 weeks. The patient should be reevaluated if reticulocytosis does not occur or if Hb does not increase by 2 g/dL within 3 weeks. Iron therapy is continued until iron stores are replenished, which usually requires at least 3 to 6 months.

- In megaloblastic anemia, signs and symptoms usually improve within a few days after starting vitamin B12 or folate therapy. Neurologic symptoms can take longer to improve or can be irreversible, but they should not progress during therapy. Reticulocytosis should occur within 2 to 5 days. A week after starting vitamin B12 therapy, Hb should rise and leukocyte and platelet counts should normalize. Hematocrit should rise 2 weeks after starting folate therapy.

- In anemia of chronic disease, reticulocytosis should occur a few days after starting epoetin alfa therapy. Iron, TIBC, transferring saturation, or ferritin levels should be monitored at baseline and periodically because iron depletion is a major reason for treatment failure. The optimal form and schedule of iron supplementation are unknown. If clinical response does not occur by 8 weeks, epoetin alfa should be discontinued.

Sickle cell

♣ **DEFINITION**: Sickle cell syndromes are hereditary disorders characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs).

♣ **PATHOPHYSIOLOGY:**

- The most common abnormal hemoglobin in the United States is hemoglobin S (HbS). Two genes for HbS result in sickle cell disease (SCD) or sickle cell anemia, which occurs in 0.3% of African Americans. One gene for HbS results in sickle cell trait, which occurs in 8% of African Americans. Hemoglobin C, another abnormality, occurs in 2% to 3% of African Americans.

- **Clinical manifestations** of SCD are attributable to impaired circulation, RBC destruction, and stasis of blood flow. These problems are attributable to disturbances in RBC polymerization and to membrane damage.
- Polymerization allows deoxygenated hemoglobin to exist as a semisolid gel that protrudes into the cell membrane, distorting RBCs into sickle shapes.
- Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels. Such obstructive events lead to local tissue hypoxia and accentuate the

pathologic process.

- Repeated cycles of sickling, upon deoxygenation, and unsickling, upon oxygenation, damage the RBC membrane and cause irreversible sickling. Rigid, sickled RBCs are easily trapped, shortening their circulatory survival and resulting in chronic hemolysis.
- Additional contributing factors include functional asplenia (and increased risk of bacterial infection), deficient opsonization, and coagulation abnormalities.

♣ CLINICAL PRESENTATION:

- SCD involves many organ systems. Clinical manifestations depend on the genotype (Table 34-1).
- Feature presentations of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4 to 6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly and, in infants, pain and swelling of the hands and feet (e.g., hand-and-foot syndrome or dactylitis).
- Usual clinical signs and symptoms of SCD are chronic anemia; fever; pallor; arthralgia; scleral icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart; and hematuria.
- Children experience delayed growth and sexual maturation, and characteristic
- Physical findings such as protuberant abdomen and exaggerated lumbar lordosis.
- Acute complications of SCD include fever and infection (e.g., sepsis caused by encapsulated pathogens such as Streptococcus pneumonia), stroke, acute Sickle Cell Disease chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
- Sickle cell crisis can be precipitated by fever, infection, dehydration, hypoxia, acidosis, sudden temperature change, or a combination of factors. The most common type is vaso occlusive or infarctive crisis, which is manifested by pain over the involved areas without change in hemoglobin.
- Aplastic crisis is characterized by decreased reticulocyte count and rapidly developing severe anemia, with or without pain. Splenic sequestration crisis is a massive enlargement of the spleen leading to hypotension, shock, and sudden death in young children. Repeated infarctions lead to
- Autosplenectomy as the disease progresses, therefore, incidence declines as adolescence approaches.
- Chronic complications involve many organs and include pulmonary hypertension, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, and hematuria and other renal complications.
- Patients with sickle cell trait are usually asymptomatic, except for rare painless hematuria.
- Chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.

Clinical Features of Sickle Cell Trait and Common Types of Sickle Cell Disease	
Type	**Clinical Features**
Sickle cell trait	Rare painless hematuria; normal Hb level; heavy exercise under extreme conditions may provoke gross hematuria and complications
Sickle cell anemia	Pain crises, microvascular disruption of organs (spleen, liver, bone bone marrow, kidney, brain, and lung), gallstone, priapism, leg ulcers, anemia (Hb 7–10 g/dL)
Sickle cell hemoglobin C	Painless hematuria and rare aseptic necrosis of bone; vasoocclusive crises are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 10–12 g/dL)

♣ **DIAGNOSIS**

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing.
- Laboratory findings include low hemoglobin; increased reticulocyte, platelet, and white blood cell counts; and sickle forms on the peripheral smear.

♣ **DESIRED OUTCOME**

- The goal of treatment is to reduce hospitalizations, complications, and mortality.

♣ **TREATMENT**

☒ GENERAL PRINCIPLES

- Patients with SCD require lifelong multidisciplinary care. Interventions include general measures, preventive strategies, and treatment of complications and acute crises.
- Patients with SCD should receive routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations.
- Prophylactic **penicillin** is recommended for children with SCD until they are 5 years old. Beginning at age 2 months or earlier, the dosage is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg twice daily until age 5 years, or benzathine penicillin, 600,000 units intramuscularly every 4 weeks from age 6 months to 6 years.
- **Folic acid**, 1 mg daily, is recommended in adult patients, pregnant women, and patients of all ages with chronic hemolysis.

☒ FETAL HEMOGLOBIN INDUCERS

- HbF directly effects polymer formation. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent crises and higher mortality.
- **Hydroxyurea**, a chemotherapeutic agent, has many effects on blood cells, including the stimulation of HbF production. It is indicated for patients with frequent painful episodes, severe symptomatic anemia, acute chest syndrome, or other severe vasoocclusive complications. The dosage should be individualized based on response and toxicity.
- Strategies being investigated to induce HbF include **butyrate** and **5-aza-2- deoxycytidine (decitabine)**.
- Chronic transfusion is indicated to prevent stroke and stroke recurrence in children. Transfusion frequency is usually every 3 to 4 weeks and should be adjusted to maintain HbS of less than 30% of total hemoglobin. The optimal duration is unknown. Risks include alloimmunization, hyperviscosity, viral transmission (requiring hepatitis A and B vaccination), volume and iron overload, and transfusion reactions.
- Allogeneic hematopoietic stem cell transplantation is the only therapy that is curative. The best candidates are younger than 16 years of age, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include mortality, graft rejection, and secondary malignancies.

☒ TREATMENT OF COMPLICATIONS

- Patients should be educated to recognize conditions that require urgent evaluation. To avoid exacerbation during acute illness, patients should maintain balanced fluid status and oxygen saturation of at least 92%.
- RBC transfusions are indicated for acute exacerbation of baseline anemia (e.g., aplastic crisis, hepatic or splenic sequestration, severe hemolysis), severe vasoocclusive episodes, and procedures requiring general anesthesia or ionic contrast. Transfusions might be beneficial in patients with complicated obstetric problems, refractory leg ulcers, refractory and protracted painful episodes, and severe priapism.
- Fever of 38.5°C (101.3°F) or higher should be evaluated promptly. A low threshold for empiric antibiotic therapy with coverage against encapsulated organisms is recommended (e.g., ceftriaxone for outpatients and cefotaxime for inpatients).
- Patients with acute chest syndrome should receive incentive spirometry; appropriate fluid therapy; broad-spectrum antibiotics including a macrolide or quinolone; and, for hypoxia or acute distress, oxygen therapy.
- Steroids and nitric oxide are being evaluated.
- Priapism has been treated with analgesics, antianxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (e.g., phenylephrine, epinephrine), and vasodilators to relax smooth muscle (e.g., terbutaline, hydralazine).

☒ TREATMENT OF SICKLE CELL CRISIS

- Treatment of aplastic crisis is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia. Antibiotic therapy is not warranted because the most common etiology is viral, not bacterial, infection.
- Treatment options for splenic sequestration include observation alone, especially for adults because they tend to have milder episodes; chronic transfusion to delay splenectomy; and splenectomy after a life-threatening crisis, after repetitive episodes, or for chronic hypersplenism.
- Hydration and analgesics are the mainstays of treatment for vasoocclusive (painful) crisis. Fluid replacement should be 1.5 times the maintenance requirement, can be administered IV or orally, and should be monitored to avoid volume overload. An infectious etiology should be considered; if appropriate, empiric therapy should be initiated.
- Analgesic therapy should be tailored to the individual because of the variable frequency and severity of pain. Pain scales should be used to quantify the degree of pain.
- Mild to moderate pain should be treated with nonsteroidal anti-inflammatory drugs or acetaminophen.
- Severe pain should be treated aggressively with an opioid, such as morphine, hydromorphone, fentanyl, and methadone. Moderate pain should be treated with a weak opioid, such as codeine or hydrocodone. Meperidine should be avoided because accumulation of the normeperidine metabolite can cause neurotoxicity, especially in patients with impaired renal function.
- Severe pain should be treated with an IV opioid titrated to pain relief and then administered on a scheduled basis with as-needed dosing for breakthrough pain. Patient-controlled analgesia is commonly utilized.
- Suspicion of addiction commonly leads to suboptimal pain control. Factors that minimize dependence include aggressive pain control, frequent monitoring, and tapering medication according to response.
- Poloxamer 188 (Flocor) is being evaluated for vasoocclusive crisis. This surfactant returns RBCs to a nonadhesive state and blocks RBC aggregation to enhance blood flow in ischemic areas.

☒ EVALUATION OF THERAPEUTIC OUTCOMES

- All patients should be evaluated regularly to establish baseline, monitor changes, and provide age-appropriate education.
- Laboratory evaluations include complete blood cell and reticulocyte counts and HbF level. Renal, hepatobiliary, and pulmonary function should be evaluated. Patients should be screened for retinopathy.
- The efficacy of hydroxyurea can be assessed by monitoring the number, severity, and duration of sickle cell crises.

Coagulation disorders

Definition:

- These are a group of disease caused due to deficiency of clotting factors and lead to defects in normal clot formation process.

Classification

- Based on origin these disorder are of two types,

1. Hereditary Coagulation Disorder

- These inherited plasma coagulation disorders are due to qualitative or quantitative defect in single coagulation factor.

a) Sex Linked (X) Disorders e.g. Classical haemophilia or haemophilia A, Christmas disease or haemophilia B

b) Autosomal Disorders e.g. von Willebrand's disease

2. Acquired Coagulation Disorder

- These are characterized by deficiency of multiple coagulation factors.

a) Vitamin K deficiency

b) Coagulation disorder of liver disease

c) Fibrinolytic defects

d) Disseminated intravascular resistance.

Hereditary coagulation disorders

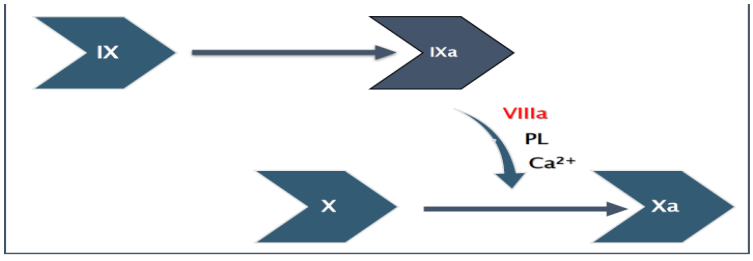
- CLASSICAL HAEMOPHILIA
- oIts is the second most common cause of hereditary coagulation disorder.
- oIt is inherited as sex (X) linked recessive trait, so more common in males while females are the carriers.

Pathogenesis:

a. Quantitative reduction in factor VIII (in 90% of cases).

b. Normal or increased level of factor VIII with reduced activity (in 10% of cases).

- Factor VIII is synthesized in hepatocytes. In the intrinsic coagulation pathway factor IXa complexes with factor VIIIa, this complex in the presence of platelets, PL and Ca2+ activates factor X to Xa.
- Disruption of the Intrinsic Coagulation Pathway (Due to the absence of activated Factor VIII).



Clinical Features:

- Symptoms are elicited when factor VIII activity is reduced to less than 25%. Patient suffers bleeding for hrs to days and severity is based on plasma level of factor VIII activity.
- Recurrent painful haemarthroses and muscle haematoma and sometimes haematuria.

Lab Diagnosis:

a. Whole blood coagulation time is raised in severe cases only.

b. Prothrombin time is usually normal.

c. Activated partial thromboplastin time (APTT or PTTK) is typically prolonged.

d. Specific assays for factor VIII shows lowered activity (50% activity of factor VIII in female carriers).

Treatment:

- Factor VIII replacement therapy (infusion of factor VIII

❑ Christmas disease/haemophilia b

- X linked recessive disease.
- Rarer than haemophilia A.
- Incidence Ratio is 1: 100000 male birth.
- Inheritance pattern and clinical features are similar to classical haemophilia.

Lab Diagnosis:

- Assay of factor IX level which is lowered. Other lab findings are similar to haemophilia A.

Treatment:

- Infusion of fresh frozen plasma or plasma enriched with factor IX.

❑ VON WILLEBRAND'S DISEASE

- Most common hereditary coagulation disorder.
- Inherited as autosomal dominant trait.
- Incidence rate is 1:1000 of either sex.
- Occurs due to qualitative or quantitative defect in vWF.
- Factor VIII-von Willebrand complex
- Consists of 99% vWF and 1% factor VIII. They circulate together as a unit and perform important function in clotting and facilitate platelet adhesion to sub endothelial collagen.

Clinical Features:

- Spontaneous bleeding from mucous membranes, excessive bleeding from nose and menorrhagia.

Types:

Type-1 disease

- It is the most common and is characterized by mild to moderate decrease in plasma vWF (50% activity). Synthesis of vWF is normal but the release of its multimers is inhibited.

Type-2 disease

- It is much less common and is characterized by normal or near levels of vWF which is functionally defective.

Type 3 disease

- It is extremely rare and is most severe form of disease.
- These patients have no detectable vW activity and may have sufficiently low level of factor VIII.

Lab Diagnosis:

- Prolonged bleeding time.
- Normal platelet count.
- Reduced plasma vWF concentration.
- Defective platelet aggregation with ristocetin, an antibiotic.
- Reduced factor VIII activity.

Treatment:

- Cryo-precipitates or Factor VIII concentrates

ACQUIRED COAGULATION DISORDERS

VITAMIN K DEFICIENCY

- Vitamin K serves as a cofactor in the formation of 6 prothrombin complex proteins (Vitamin K dependent coagulation factors) synthesized in the liver: Factor II, VII, IX, X, Protein C and Protein S.

Causes of Vitamin K deficiency:

- Obstructive jaundice.
- Chronic diarrhoea.
- Liver disease.
- Haemorrhagic states in infants.

♣ **Lab Diagnosis:**

- Prolonged PTT and PTTK.

♣ **Treatment:**

- Parenteral administration of Vitamin K causes
- complete recovery in 48 hrs.

❑ **Coagulation disorder in liver disease**

- Liver is the site of synthesis and metabolism of Coagulation Factors.
- Liver disease leads to hypercoagulability and predispose to develop DIC and systemic fibrinolysis.

Factors promoting Coagulation	Factors inhibiting coagulation
Synthesis of Coagulation Factors.	Synthesis of Coagulation Factors. Synthesis of Anti-thrombin 3, Protein C and Protein S
Clearance of Fibrinolytic enzymes	Clearance of Activated Factors

▪ **Major causes of bleeding in liver disease are:**

- Morphologic lesions:
- Portal hypertension, peptic ulceration, gastritis.
- Hepatic dysfunction:
- Impaired hepatic synthesis of coagulation factors and coagulation inhibitors, impaired absorption and metabolism of Vitamin K, failure to clear activated coagulation factors.
- Complication of therapy
- Massive transfusion leading to platelet and clotting factors dilution, following heparin therapy.

♣ **Lab Diagnosis:**

- Prolonged PTT and PTTK, mild thrombocytopenia, normal fibrinogen level and decreased hepatic stores of Vitamin k.

❑ Disseminated intravascular coagulation

- Also called as defibrinate syndrome or consumption coagulopathy is a complex thrombo-haemorrhagic disease occurring as secondary complication of some systemic disease.
- Disseminated intravascular coagulation (DIC) is a disorder characterized by both acute generalized, widespread activation of coagulation, which results in thrombotic complications due to the intravascular formation of fibrin, and diffuse hemorrhages, due to the consumption of platelets and coagulation factors. Systemic activation of coagulation

may occur in a variety of disorders, including sepsis, severe infections, malignancies, obstetric or vascular disorders, and severe toxic or immunological reactions.

♣ **Major disorders associated with DIC:**

- Obstetrics Complications- Abruption placentae, retained dead foetus, septic abortion, amniotic fluid embolism, toxaemia.
- Infections- Gram negative sepsis, meningococcemia, rocky mountain spotted fever, malaria.
- Neoplasms- Carcinoma of pancreas, prostate, lung and stomach.
- Massive Tissue Injury- Traumatic, burns, extensive surgery.
- Miscellaneous- Acute intravascular haemolysis, snake bite, giant haemangioma, shock, heat stroke.

♣ **Pathogenesis:**

- Disseminated intravascular coagulation usually results from exposure of tissue factor to blood, initiating the coagulation cascade. In addition, the fibrinolytic pathway is activated in DIC.
- Stimulation of endothelial cells by cytokines and perturbed microvascular blood flow causes the release of tissue plasminogen activator (tPA) from endothelial cells.
- Both tPA and plasminogen attach to fibrin polymers, and plasmin (generated by tPA cleavage of plasminogen) cleaves fibrin into D-dimers and other fibrin degradation products.
- DIC can, therefore, cause both thrombosis and bleeding (if the consumption of platelets and/or coagulation factors is excessive)

♣ **Clinical Features:**

1. Widespread fibrin deposition within microcirculation leading to ischemia of organs like kidney and brain.
2. Bleeding diathesis- ensues as the platelets and clotting factors are consumed and there are secondary release of plasminogen activator but also digest Factor V and VIII there by reducing their concentration further.

♣ **Lab Diagnosis:**

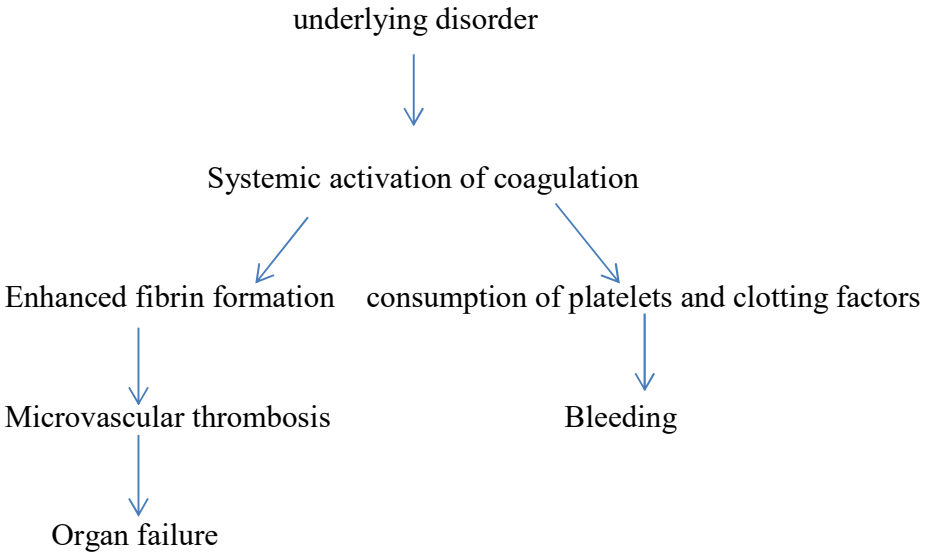
a. Reduced platelet count.

b. Blood film shows microangiopathic haemorrhagic haemolytic anaemia.

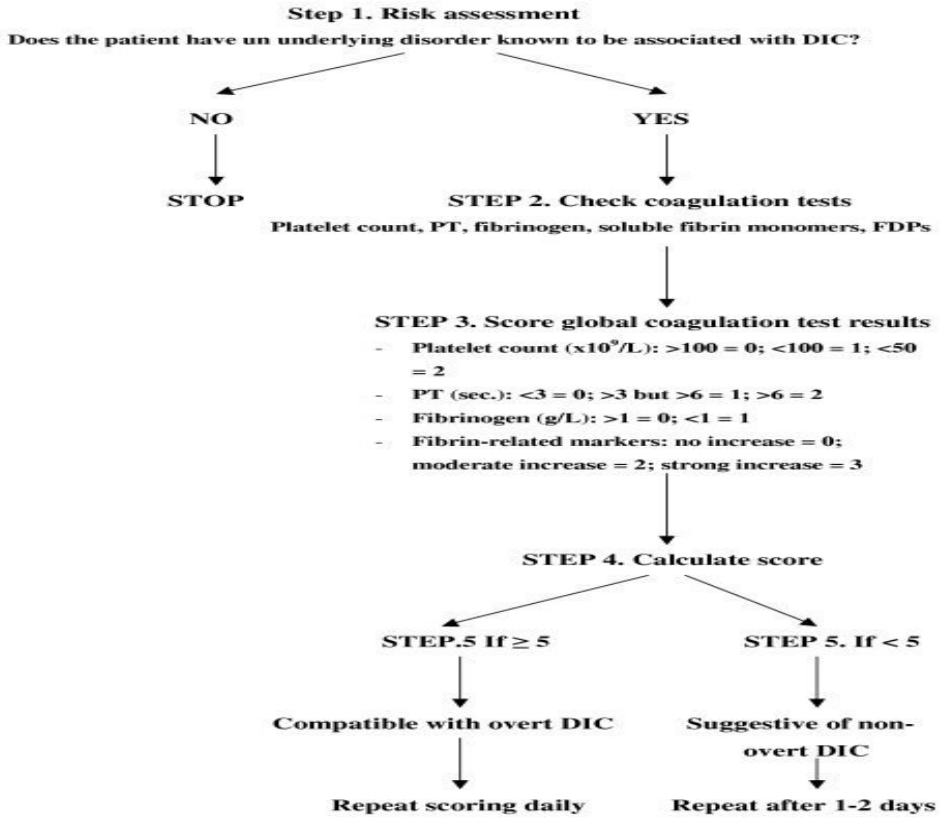
c. PT, TT,APTT are prolonged.

d. Plasma fibrinogen level is reduced.

♣ **Clinical manifestations of coagulation abnormalities in disseminated intravascular coagulation.**



❑ **Five-step algorithm for the diagnosis of disseminated intravascular coagulation.**



♣ **Treatment:**

- Anticoagulants like heparin or coagulants contained in fresh frozen plasma, underlying disorder must be treated simultaneously.

Treatment modalities for disseminated intravascular coagulation.

1) Replacement therapy	**- Fresh-frozen plasma**
2) Anticoagulants	- Unfractionated and low-molecular-weight heparin
	- Recombinant hirudin
	- Recombinant tissue factor pathway inhibitor
	- Recombinant nematode anticoagulant protein c2
3) Restoration of anticoagulant pathways	**- Antithrombin**
	- Recombinant human activated protein C
4) Other agents	**- Recombinant activated factor VII**
	- Antifibrinolytic agents
	- Antiselectin antibodies
	- Recombinant interleukin-10
	- Monoclonal antibodies against TNF and CD14