Hypertension

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Hypertension
Introduction

1- Hypertension is defined as **persistently elevated arterial blood pressure** (BP).

(See Table -1 for the classification of BP in adults).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
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<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>or 80–89</td>
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<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>or 90–99</td>
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<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
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</table>

2- **Isolated systolic hypertension** is diastolic blood pressure (DBP) <80 mm Hg and systolic blood pressure (SBP) ≥130 mm Hg.

3- **Hypertensive crisis** (BP >180/120 mm Hg) is categorized as **hypertensive emergency** (extreme BP elevation with acute or progressing end-organ damage) or **hypertensive urgency** (extreme BP elevation without acute or progressing end-organ injury).
Pathophysiology

1- Hypertension may result from an unknown etiology (primary or essential hypertension) or from a specific cause (secondary hypertension).

2- Secondary hypertension (<10% of cases) is usually caused by chronic kidney disease (CKD) or renovascular disease.

3- Examples of drugs that may increase BP include corticosteroids, estrogens, NSAIDs, cyclosporine, erythropoietin, and venlafaxine.
Pathophysiology

4-Factors contributing to development of primary hypertension include: **Humoral abnormalities** [involving the renin–angiotensin–aldosterone system (RAAS)], **disturbances in the CNS**, **Abnormalities in renal system**, **Deficiency in synthesis of vasodilating substances** in vascular endothelium or **excess vasoconstricting substances**, and **high sodium intake or lack of dietary calcium**.

5-Major causes of death include cerebrovascular events, cardiovascular (CV) events, and renal failure. Probability of premature death correlates with the severity of BP elevation.
Clinical presentation and diagnosis

1- Patients with uncomplicated primary hypertension are usually asymptomatic initially.

2- Patients with secondary hypertension may have symptoms of the underlying disorder.

3- Elevated BP may be the only sign of primary hypertension on physical examination.

4- Diagnosis should be based on the average of two or more readings taken at each of two or more clinical encounters.

5- Signs of end-organ damage occur primarily in the eyes, brain, heart, kidneys, and peripheral vasculature.

6- Laboratory tests: Blood urea nitrogen (BUN), serum creatinine with estimated glomerular filtration rate (eGFR), fasting lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium, calcium), uric acid, hemoglobin and hematocrit, and spot urine albumin-to-creatinine ratio. A 12-lead electrocardiogram (ECG) should also be obtained.
Treatment

1-Goals of Treatment: The overall goal is to reduce morbidity and mortality from CV events. The 2017 ACC/AHA guideline recommends a goal BP of <130/80 mm Hg for most patients.

2-For older ambulatory, community-dwelling patients, the goal is SBP <130 mm Hg. For institutionalized older patients and those with a high disease burden or limited life expectancy, consider a relaxed SBP goal of <150 mm Hg (or <140 mm Hg if tolerated).

American College of Cardiology/American Heart Association (ACC/AHA)
Nonpharmacologic Therapy

A-Implement lifestyle modifications in all patients with elevated BP or stage 1 or 2 hypertension.

B-These measures alone are appropriate initial treatment for patients with elevated BP or stage 1 hypertension who are at low risk of ASCVD (ie, primary prevention with a 10-year ASCVD risk <10%). Start drug therapy for these patients when BP is ≥140/90 mm Hg.

C-For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or an elevated 10-year ASCVD risk ≥10%, the threshold for starting drug therapy is ≥130/80 mm Hg with a goal BP of <130/80 mm Hg.
Nonpharmacologic Therapy

D-Lifestyle modifications shown to lower BP include:

(1) **weight loss** if overweight or obese,

(2) the Dietary Approaches to Stop Hypertension (DASH) eating plan,

(3) **reduced salt intake**, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride),

(4) **physical activity** (90–150 min/week of aerobic or dynamic resistance training), and

(5) **moderation of alcohol intake** (≤2 drinks/day in men and ≤1 drink/day in women).

Although **smoking** cessation does not control BP, it reduces CV disease risk and should be encouraged.
Pharmacologic Therapy

General Approach to Treatment

1-Initial drug selection depends on the degree of BP elevation and presence of compelling indications for certain drugs.

2-Use a single first-line drug as initial therapy in most patients with newly diagnosed stage 1 hypertension.

3-Start combination drug therapy (preferably with two first-line drugs) as the initial regimen in patients with newly diagnosed stage 2 hypertension.
Pharmacologic Therapy

- General Approach to Treatment

4-The **four first-line options** are angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and **thiazide diuretics**.

5-**β-Blockers** should be reserved to treat a **specific compelling indication** or in **combination** with a first-line antihypertensive agent for patients without a compelling indication.

6-Other **antihypertensive** drug classes (α1-blockers, direct renin inhibitors, central α2-agonists, and direct arterial vasodilators) may be used for select patients **after implementing first-line agents**.
Pharmacologic Therapy

Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled trial. 2 = Evidence from at least one well-designed clinical trial with randomization; from cohort or case-controlled analytic studies; or dramatic results from uncontrolled experiments or subgroup analyses. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.)
Compelling Indications

- Compelling indications are specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication. Selection of drug therapy should follow an evidence-based order.
Compelling Indications

1. **Left Ventricular Function**
   - **Standard Pharmacotherapy**
     - Diuretic with ACE inhibitor [A-1]; then add β-Blocker [A-1]
   - **Add-on Pharmacotherapy**
     - ARB [A-2] or aldosterone antagonist [A-2]

2. **Postmyocardial Infarction**
   - **Standard Pharmacotherapy**
     - β-Blocker [A-1]; then add ACE inhibitor [A-1] or ARB [A-2]

3. ** Coronary Disease**
   - **Standard Pharmacotherapy**
     - β-Blocker [A-1]; then add ACE inhibitor [A-1] or ARB [A-2]

4. **Diabetes Mellitus**
   - **Standard Pharmacotherapy**
     - ACE inhibitor [A-1]; or ARB [A-2]

5. **Chronic Kidney Disease**
   - **Standard Pharmacotherapy**
     - ACE inhibitor [A-1]; or ARB [A-1]

6. **Recurrent Stroke Prevention**
   - **Standard Pharmacotherapy**
     - Diuretic with ACE inhibitor [A-2] or ARB [A-2]
Heart Failure with *Reduced Ejection Fraction* (HFrEF)

- Heart failure is a clinical syndrome characterized by dyspnea or exertional limitation due to impairment of ventricular filling or ejection of blood or both.
- HF has increased to an estimated 23 million people, and approximately 50% of cases are HF with reduced ejection fraction.
- HFrEF occurs when the left ventricular ejection fraction (LVEF) is 40% or less and is accompanied by progressive left ventricular dilatation and adverse cardiac remodeling.
**A-Heart Failure with Reduced Ejection Fraction (HFrEF)**

**Heart Failure with Ejection Fraction Explained**

Ejection fraction is the percentage of blood pumped out by one's heart to the rest of the body, and heart failure with reduced ejection fraction (HFrEF) is a type of heart failure where the ejection fraction is measured at less than 40%.

**Formula:**

\[
\text{Ejection Fraction (EF)} = \frac{\text{Amount of Blood Pumped Out}}{\text{Amount of Blood in the Chamber}}
\]

- **Preserved EF**
  - 55-70%
  - Is pumped out at each heart beat.

- **Mid-Range EF**
  - 41-49%
  - Is pumped out at each heart beat.

- **Reduced EF**
  - \(\leq 40\%\)
  - Is pumped out at each heart beat.
A-Heart Failure with Reduced Ejection Fraction (HFrEF)

- Cardiomyocytes dysfunction;
- Metabolic alterations;
- Inflammation (low grade);
- Aging;
- Autophagy?

HFrEF

- Cardiomyocytes loss;
- Sarcomeric disarrangement;
- Inflammation (high grade);
- Autophagy
A-Heart Failure with Reduced Ejection Fraction (HFrEF)

1-Guideline-directed medical therapy consists of three to four drugs: **ACE inhibitor or ARB** plus **diuretic**, followed by addition of an evidence-based **β-blocker** and possibly a **mineralocorticoid receptor antagonist**.

2-Start an **ACE inhibitor or ARB** in **low doses** to avoid **orthostatic hypotension** because of the high renin state in HF.

3-Diuretics reduce **edema**, and **loop diuretics** are often needed, especially in patients with advanced HF and/or CKD.

4-**β-Blockers** are part of **standard treatment**. Because of the risk of **exacerbating** HF, β-blockers must be started in **very low doses** and titrated slowly to high doses based on **tolerability**.

5-**Bisoprolol, carvedilol, and metoprolol** succinate are the only β-blockers **proven** to be beneficial in HFrEF.

6-After implementation of a standard three-drug regimen, other agents may be added to further reduce **CV morbidity** and mortality, and reduce BP if needed. A **mineralocorticoid receptor antagonist** (spironolactone or eplerenone) may be considered at this point.
**B-Heart Failure with Preserved Ejection Fraction (HFpEF)**

1-Unlike interventions in HFrEF that decrease morbidity and mortality, trials using the same medications in HFpEF have not shown similar benefits.

2-Therefore, treatment should be targeted at signs and symptoms (eg, dyspnea, fatigue, edema), appropriate management of underlying coronary artery disease, and attainment of goal BP to prevent HF progression.

3-Patients should use a β-blocker or an ACE inhibitor (or ARB) for treatment of hypertension, and they should receive a diuretic if signs and symptoms of edema are present.
C-Stable Ischemic Heart Disease (SIHD)

1-β-Blockers are first-line therapy in SIHD; they reduce BP and improve angina symptoms by decreasing myocardial oxygen consumption and demand.

2-β-Blockers should be used for hypertension treatment in patients with SIHD. An ACE inhibitor or ARB has been shown to reduce CV events as an add-on to a β-blocker.

3-A long-acting nondihydropyridine CCB (Diltiazem) is an alternative to a β-blocker in SIHD, but β-blockers are the therapy of choice. A dihydropyridine CCB (Amlodipine) may be considered as add-on therapy in SIHD patients who have ongoing ischemic symptoms (but cardiac stimulation makes these agents less desirable).
C-Stable Ischemic Heart Disease (SIHD)

4-For acute coronary syndromes, first-line therapy includes a β-blocker and ACE inhibitor (or ARB).
D-Diabetes Mellitus

1-All four first-line antihypertensive classes (ACE inhibitors, ARBs, CCBs, thiazides) reduce CV events in patients with diabetes, with no evidence of difference in all-cause mortality, CV mortality, HF, or stroke.

2-The risk of kidney disease progression is low in the absence of albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g [3.4 mg/mmol creatinine]). Therefore, any first-line agent can be used to control hypertension in patients with diabetes in the absence of albuminuria.
3-Regardless of the initial agent selected, most patients require combination therapy, which typically includes an ACE inhibitor (or ARB) with a CCB or thiazide.

4-After first-line agents, a β-blocker is a useful add-on therapy for BP control in patients with diabetes. However, they may mask symptoms of hypoglycemia (tremor, tachycardia, and palpitations but not sweating) in tightly controlled patients, and delay recovery from hypoglycemia. Despite these potential problems, β-blockers can be used safely in patients with diabetes.
1-In addition to lowering BP, ACE inhibitors and ARBs reduce intraglomerular pressure, which may further slow CKD progression.

2-Start with low doses and evaluate the serum creatinine soon after starting therapy to minimize the risk of rapid and profound BP drops that could precipitate acute kidney injury (AKI).
F-Secondary Stroke Prevention

1-A thiazide diuretic, either alone or combined with an ACE inhibitor, is recommended for patients with history of stroke or transient ischemic attack.

2-The threshold for starting antihypertensive drug therapy in patients with a history of stroke is when BP is >140/90 mm Hg (goal of <130/80 mm Hg).
1- Angiotensin-Converting Enzyme Inhibitors (ACE)

- (captopril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, and trandolapril)

1-ACE inhibitors block **conversion** of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion.

2-Starting doses should be **low with slow dose titration**. Acute hypotension may occur at the onset of therapy.

3-ACE inhibitors decrease aldosterone and can **increase serum potassium** concentrations. **Hyperkalemia** occurs primarily in patients with CKD or those also taking potassium supplements, potassium-sparing diuretics, mineralocorticoid receptor antagonists, ARBs, or direct renin inhibitors.
1- Angiotensin-Converting Enzyme Inhibitors (ACE)

4- **AKI is an uncommon but serious side effect**; preexisting kidney disease increases risk. Bilateral renal artery stenosis or unilateral stenosis renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making them particularly susceptible to AKI.

5- Serum creatinine concentrations often increase, but **modest elevations** (eg, absolute increases $<1$ mg/dL) **do not warrant treatment changes**. Discontinue therapy or reduce dose if larger increases occur.

6- **Angioedema occurs in $<1\%$ of patients.** Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation to support respiration.
1- Angiotensin-Converting Enzyme Inhibitors (ACE)

7-An ARB can generally be used in patients with a history of ACE inhibitor-induced angioedema, with careful monitoring.

8-A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.

9-ACE inhibitors (as well as ARBs and direct renin inhibitors) are contraindicated in pregnancy.
2- Angiotensin II Receptor Blockers (ARB)

- (candesartan, irbesartan, losartan, olmesartan, and valsartan…….)

1- The ARBs directly **block** the angiotensin II type 1 receptor that mediates the effects of angiotensin II.

2- Unlike ACE inhibitors, **ARBs do not block bradykinin breakdown and this accounts for the lack of cough as a side effect.**

3- The combination of an ACE inhibitor and ARB has **no additional benefit** but is associated with a higher risk of side effects and should be avoided.

4- ARBs have a low incidence of side effects. Like ACE inhibitors, they may cause renal **insufficiency, hyperkalemia, and orthostatic hypotension.**
3- Calcium Channel Blockers

1- Dihydropyridine and nondihydropyridine CCBs are first-line antihypertensive therapies and are also used in addition to or instead of other first-line agents for the compelling indication of ischemic heart disease.

2- Dihydropyridine CCBs may cause reflex sympathetic activation, and all agents (except amlodipine and felodipine) may have negative inotropic effects.

3- Verapamil decreases heart rate, slows atrioventricular (AV) nodal conduction, and produces a negative inotropic effect that may precipitate HF in patients with borderline cardiac reserve. Diltiazem decreases AV conduction and heart rate to a lesser extent than verapamil.
3- Calcium Channel Blockers

4- Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia, AV block, and HF. Both can cause peripheral edema and hypotension. Verapamil causes constipation in about 7% of patients.

5- Dihydropyridines cause a baroreceptor-mediated reflex increase in heart rate because of potent peripheral vasodilating effects. Dihydropyridines do not decrease AV node conduction and are not effective for treating supraventricular tachyarrhythmias.

6- Short-acting nifedipine may rarely increase frequency, intensity, and duration of angina in association with acute hypotension. This effect may be obviated by using sustained-release formulations of nifedipine or other dihydropyridines.

7- Other side effects of dihydropyridines are dizziness, flushing, headache, gingival hyperplasia, and peripheral edema.
4- Diuretics

1- **Thiazides** are the preferred type of diuretic and are a **first-line** option for most patients with hypertension. **Chlorthalidone** (thiazide-like) is preferred over hydrochlorothiazide, especially in resistant hypertension, because it is more potent on a milligram-per-milligram basis.

2- **Loop diuretics** (Furosemide, Bumetanide and Torasemide) are more potent for inducing diuresis but are not ideal antihypertensives unless **edema** treatment is also needed. Loop diuretics are sometimes required over thiazides in patients with severe **CKD when eGFR is <30 mL/min/1.73 m²**, especially when edema is present.
4- Diuretics

3-Potassium-sparing diuretics are weak antihypertensives when used alone and provide minimal additive effect when combined with a thiazide or loop diuretic. Their primary use is in combination with another diuretic to counteract potassium-wasting properties.

4-Mineralocorticoid receptor antagonists (spironolactone and eplerenone) are also potassium-sparing diuretics that are usually used to treat resistant hypertension because elevated aldosterone concentrations are prevalent in this setting. They are also used as add-on agents in patients with HFrEF with or without concomitant hypertension.

5-Acutely, diuretics lower BP by causing diuresis. With chronic therapy, reduced peripheral vascular resistance is responsible for persistent hypotensive effects.
4- Diuretics

6- Combining diuretics with other antihypertensive agents usually results in an additive hypotensive effect because of independent mechanisms of action. Furthermore, many nondiuretic antihypertensive agents induce sodium and water retention, which is counteracted by concurrent diuretic use.

7- Side effects of thiazides include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction.

8- Loop diuretics have less effect on serum lipids and glucose, but hypokalemia is more pronounced, and hypocalcemia may occur.
4- Diuretics

9- **Hypokalemia and hypomagnesemia** may cause muscle fatigue or cramps, and severe electrolyte abnormalities may result in serious cardiac arrhythmias. Low-dose therapy causes less electrolyte disturbances than higher doses.

10- **Potassium-sparing diuretics** may cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with a mineralocorticoid receptor antagonist, ACE inhibitor, ARB, direct renin inhibitor, or potassium supplement.

11- **Spironolactone** may cause gynecomastia in up to 10% of patients; this effect occurs rarely with eplerenone.
5- β-Blockers

1-Evidence suggests that β-blockers may not reduce CV events as well as ACE inhibitors, ARBs, CCBs, or thiazides when used as the initial drug in patients who do not have a compelling indication for a β-blocker.

2-β-Blockers are appropriate first-line agents when used to treat specific compelling indications or when an ACE inhibitor, ARB, CCB, or thiazide cannot be used.

3-β-Blockers also have an important role as add-on therapy to first-line agents in patients with hypertension but no compelling indications.

4-Atenolol, betaxolol, bisoprolol, metoprolol, and nebivolol are β1-cardioselective at low. As a result, they are less likely to provoke bronchospasm and vasoconstriction and are safer than nonselective β-blockers in patients with asthma or diabetes who have a compelling indication for a β-blocker. Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.
5- β-Blockers

5-Acebutolol, carteolol, and pindolol possess *intrinsic sympathomimetic activity* (ISA) or *partial β-receptor agonist activity*. Theoretically, these drugs may have advantages in select patients with HF or sinus bradycardia. Unfortunately, they do not reduce CV events as well as other β-blockers and may increase CV risk in patients with SIHD. Thus, agents with ISA are rarely needed and have no role in hypertension management.

6-Atenolol and nadolol have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with renal insufficiency.

7-Even though the half-lives of other β-blockers are shorter, once-daily administration still may be effective.
5- β-Blockers

8-Cardiac side effects include bradycardia, AV conduction abnormalities, and acute HF. Blocking β2-receptors in arteriolar smooth muscle may cause cold extremities and aggravate intermittent claudication or Raynaud phenomenon because of decreased peripheral blood flow.

9-Increases in serum lipids and glucose appear to be transient and of little clinical significance.

10-Abrupt cessation of β-blocker therapy can produce cardiac ischemia (angina, chest pain), a CV event, or even death in patients with coronary artery disease. In patients without heart disease, abrupt discontinuation of β-blockers may be associated with tachycardia, sweating, and generalized malaise in addition to increased BP. For these reasons, the dose should always be tapered gradually over 1–2 weeks before discontinuation.
6- α1-Receptor Blockers

1- Prazosin, terazosin, and doxazosin are selective α1-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation and BP lowering.

2- A first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope may occur within 1–3 hours of the first dose or after later dosage increases.

3- The patient should take the first dose (and subsequent first increased doses) at bedtime. Occasionally, orthostatic hypotension persist with chronic administration.

4- Sodium and water retention can occur; these agents are most effective when given with a thiazide to maintain antihypertensive efficacy and minimize edema.

5- These agents block postsynaptic α1-adrenergic receptors on the prostate capsule, causing relaxation and decreased resistance to urinary outflow. Although they can provide symptomatic benefit in men with benign prostatic hyperplasia, they should be used to lower BP only in combination with first-line antihypertensive agents.
7- Direct Renin Inhibitor

- **Aliskiren** blocks the Renin-Angiotensin-Aldosterone System (RAAS) at its point of activation, resulting in reduced plasma renin activity and BP. It is approved for monotherapy or in combination therapy. *Its role in the management of hypertension is limited.*
8- Central $\alpha_2$-Agonists

1- Clonidine, guanfacine, and methyldopa lower BP primarily by stimulating $\alpha_2$-adrenergic receptors in the brain.

2- Clonidine is often used in resistant hypertension, and methyldopa is frequently used for pregnancy-induced hypertension.

3- Chronic use results in sodium and fluid retention. Other side effects include depression, orthostatic hypotension, dizziness, and anticholinergic effects (eg, dry mouth, sedation). Abrupt cessation may lead to rebound hypertension.

4- Methyldopa rarely causes hepatitis or hemolytic anemia. A transient elevation in hepatic transaminases occasionally occurs. Discontinue therapy if persistent increases in liver function tests occur, because this may herald onset of fulminant, life-threatening hepatitis. Coombs-positive hemolytic anemia occurs rarely, and 20% of patients exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited usefulness except in pregnancy.
9- Direct Arterial Vasodilators

1- **Hydralazine** and **minoxidil** directly relax arteriolar smooth muscle, resulting in vasodilation and BP lowering. Compensatory activation of baroreceptor reflexes increases sympathetic outflow, thereby increasing heart rate, cardiac output, and renin release. Consequently, hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a diuretic and a β-blocker.

2-**Direct vasodilators** can precipitate angina in patients with underlying SIHD unless the baroreceptor reflex mechanism is blocked with a β-blocker. Nondihydropyridine CCBs can be used as an alternative to β-blockers in patients with contraindications to β-blockers.
9- Direct Arterial Vasodilators

3-Hydralazine may cause a dose-related, reversible lupus-like syndrome, which is more common in slow acetylators. Lupus-like reactions can usually be avoided by limiting the maximum total daily dose to 200 mg. Because of side effects, hydralazine has limited usefulness for chronic hypertension management.

4-Minoxidil cause reversible hypertrichosis on the face, arms, back, and chest may be troublesome. Minoxidil is reserved for resistant hypertension and for patients requiring hydralazine who experience drug-induced lupus.
Special Populations
1- Older Persons

1- Older patients may present with either isolated systolic hypertension or elevation in both SBP and DBP. CV morbidity and mortality are more directly correlated to SBP than to DBP in patients aged 50 and older.

2- First-line antihypertensives provide significant benefits and can be used safely in older patients, but **smaller-than-usual initial doses** must be used for initial therapy.
2- Children and Adolescents

1-In children, hypertension is defined as SBP or DBP that is >95th percentile for sex, age, and height on at least three occasions. For adolescents, BP values between the 90th and 95th percentile, or >120/80 mm Hg, is considered elevated BP.

2-Because secondary hypertension is more common in children and adolescents than in adults, an appropriate workup is required if elevated BP is identified.

3-Nonpharmacologic treatment is the cornerstone of therapy for primary hypertension.

4-ACE inhibitors, ARBs, β-blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.
3- Pregnancy

1- **Preeclampsia** is defined as hypertension (elevated BP $\geq 140/90$ mm Hg on more than 2 occasions at least 4 hours apart after 20 weeks’ gestation or $\geq 160/110$ mm Hg confirmed within a short interval) in association with thrombocytopenia, impaired liver function, new-onset renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. It can lead to **life-threatening complications** for both mother and fetus.

2- **Eclampsia** is the onset of convulsions in preeclampsia and is a medical emergency.

3- Definitive treatment of preeclampsia is **delivery**, and labor induction is indicated if eclampsia is imminent or present. Otherwise, management consists of restricting activity, bed rest, and close monitoring. Salt restriction or other measures that contract blood volume should be avoided.
3- Pregnancy

4-Antihypertensives are used before induction of labor if DBP is >105 mm Hg, with a target DBP of 95–105 mm Hg. Intravenous (IV) hydralazine is most commonly used; IV labetalol is also effective.

5-Chronic hypertension is hypertension that predates pregnancy. Labetalol, long-acting nifedipine, or methyldopa is recommended as first-line therapy due to favorable safety profiles. β-Blockers (except atenolol) and CCBs are also reasonable alternatives.
4- African Americans

1- Hypertension is more common and more difficult to control in African Americans than in those of other races; treatment usually requires two or more antihypertensives to reach a BP goal of $<130/80$ mm Hg.

2- CCBs and thiazides are most effective in African Americans and should be first-line in the absence of a compelling indication.
5- Pulmonary Disease and Peripheral Arterial Disease (PAD)

1-Although β-blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and COPD because of fear of inducing bronchospasm, **cardioselective β-blockers can be used safely.**

2-β-Blockers can theoretically be problematic in patients with PAD because of possible decreased peripheral blood flow secondary to unopposed stimulation of α1-receptors that results in vasoconstriction. However, **available data indicate that β-blockers do not worsen claudication symptoms or cause functional impairment.** Therefore, **antihypertensive treatment for patients with PAD should follow the same general principles as patients without PAD.**
6- Hypertensive Urgencies and Emergencies

1- Hypertensive urgencies are ideally managed by adjusting maintenance therapy, adding a new antihypertensive, increasing the dose of a current medication, or treating anxiety as applicable.

2- Acute administration of a short-acting oral drug (captopril, clonidine, or labetalol) followed by careful observation for several hours to ensure a gradual BP reduction is an option.

3- Hypertensive emergencies require immediate BP reduction with a parenteral agent to limit new or progressing end-organ damage. Nitroprusside is the agent of choice for minute-to-minute control in most cases.
Evaluation of therapeutic outcomes
Evaluation of therapeutic outcomes

1-Encourage patients to obtain a home BP monitor, record the results, and bring them to follow-up clinic visits.

2-Evaluate BP response in the clinic 4 weeks after initiating or making changes in therapy and compare the results to home BP readings.

3-Once goal BP is obtained, monitor BP every 3–6 months, assuming no signs or symptoms of acute end-organ damage. Evaluate more frequently in patients with a history of poor control, nonadherence, progressive end-organ damage, or symptoms of adverse drug effects.

4-Automated BP monitoring can be useful to establish effective 24-hour control and confirm white coat or masked uncontrolled hypertension.
Evaluation of therapeutic outcomes

5-Monitor patients routinely for adverse drug events, which may require dosage reduction or substitution with an alternative antihypertensive agent.

A-Perform laboratory monitoring 4 weeks after starting a new agent or dose increase, and then every 6–12 months in stable patients.

B-For patients treated with eplerenone or spironolactone monitor potassium concentrations and kidney function within 3 days of initiation and again at 1 week to detect potential hyperkalemia.
Evaluation of therapeutic outcomes

6-Monitor patients for signs and symptoms of hypertension-associated complications.

A-Take a careful history for ischemic chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance.

B-Monitor funduscopic changes on eye examination, LV hypertrophy on ECG, albuminuria, and changes in kidney function periodically.

7-Assess patient adherence with the regimen regularly. Ask patients about changes in their general health perception, physical functioning, and overall satisfaction with treatment.
Ischemic Heart Disease

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Ischemic Heart Disease
Introduction

1-Ischemic heart disease (IHD) is defined as lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction.

2-It may present as acute coronary syndrome (ACS), which includes unstable angina and non–ST-segment elevation (NSTEMI) or ST-segment elevation (STEMI) myocardial infarction (MI), chronic stable exertional angina, ischemia without symptoms, microvascular angina, or ischemia due to coronary artery vasospasm (variant or Prinzmetal angina).
Pathophysiology

1-Angina pectoris usually results from increased myocardial oxygen demand (MVO2) in the setting of a fixed decrease in myocardial oxygen supply because of atherosclerotic plaque.

2-Major determinants of MVO2 are heart rate (HR), myocardial contractility, and intramyocardial wall tension during systole. A doubling in any of these individual parameters requires a 50% increase in coronary flow to maintain myocardial supply.

3-Coronary plaques that occupy less than 50%–70% of the vessel luminal diameter rarely produce ischemia or angina. However, smaller plaques have a lipid-rich core and thin fibrous cap and are more prone to rupture and cause acute thrombosis.
Pathophysiology

4-When the luminal diameter of epicardial vessels is reduced by 70% or more, minimal physical exertion may result in a flow deficit with myocardial ischemia and often angina.

5-**Inflammation** also plays a role in IHD; macrophages and T-lymphocytes produce growth factors that cause proliferation of vascular smooth muscle cells. **C-reactive protein (CRP)** may be elevated and correlates with adverse cardiovascular events.

6-Ischemic episodes may be more common in the morning hours (due to circadian release of vasoconstrictors) and be precipitated by cold exposure and emotional or mental stress.

7-Patients with **variant (Prinzmetal)** angina usually do not have a coronary flow-obstructing plaque but instead have significant reduction in myocardial oxygen supply due to **vasospasm in epicardial vessels**.
Clinical presentation

1-Patients typically complain of chest pain precipitated by exertion or activities of daily living that is described as squeezing, crushing, heaviness, or chest tightness. It can also be more vague and described as a numbness or burning in the chest.

2-The location is often substernal and may radiate to the right or left shoulder or arm (left more commonly), neck, back, or abdomen. Ischemic symptoms may be associated with diaphoresis, nausea, vomiting, and dyspnea.

3-Chest pain generally lasts from 5 to 20 minutes and is usually relieved by rest or sublingual nitroglycerin (SL NTG).
Clinical presentation

4-Some patients (especially women and older individuals) present with atypical chest pain, characterized by midepigastric discomfort, effort intolerance, dyspnea, and excessive fatigue. Patients with diabetes mellitus may have decreased pain sensation due to neuropathy.

5-Patients with variant (Prinzmetal) angina are typically younger and may present with chest pain at rest, often early in the morning, and may have transient ST-segment elevation on the ECG.
Diagnosis

1-Obtain the medical history to identify the quality and severity of chest pain, precipitating factors, location, duration, pain radiation, and response to nitroglycerin or rest.

2-Ischemic chest pain may resemble pain from noncardiac sources, and diagnosis of anginal pain may be difficult based on history alone.

3-Assess nonmodifiable risk factors for coronary artery disease (CAD): age, sex, and family history of premature atherosclerotic disease in first degree relatives (male onset before age 55 or female before age 65). Identify the presence of modifiable CAD risk factors: hypertension, diabetes mellitus, dyslipidemia, and cigarette smoking.

4-Physical exam findings are usually nonspecific, but patients having an ischemic episode may present with tachycardia, diaphoresis, shortness of breath, nausea, vomiting, and lightheadedness.
Diagnosis

5-Other findings related to CAD risk factors may include increased BP. Other positive findings may include pulmonary crackles in patients with heart failure with reduced ejection fraction (HFrEF).

6-Markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP), may be elevated. Cardiac troponin concentrations are not typically elevated in stable IHD.

7-Resting ECG is normal in at least half of patients with angina who are not experiencing acute ischemia. About 50% of patients develop ischemic ECG changes during an episode of angina, which can be observed on the ECG during an exercise stress test.

8-Coronary angiography is the most accurate test for confirming CAD but is invasive and requires arterial access. Myocardial perfusion imaging, cardiac magnetic resonance, and CT angiography can also be used to detect CAD.
Treatment

Goals of Treatment:

1-A primary goal of therapy is complete (or nearly complete) elimination of anginal chest pain and return to normal activities.

2-Long-term goals are to slow progression of atherosclerosis and prevent complications such as MI, heart failure, stroke, and death.
Treatment

Nonpharmacologic Therapy

1-Lifestyle modifications include daily physical activity, weight management, dietary therapy (reduced intake of saturated fats, trans-fatty acids, and cholesterol), smoking cessation, psychological interventions (eg, screening and treatment for depression if appropriate), limitation of alcohol intake, and avoiding exposure to air pollution.

2-Surgical revascularization options for select patients include coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with or without stent placement.
Treatment

Nonpharmacologic Therapy

Revascularisation

<table>
<thead>
<tr>
<th>CABG (BYPASS SURGERY)</th>
<th>STENTING (PTCA OR PCI)</th>
</tr>
</thead>
</table>

- **CABG (BYPASS SURGERY)**
  - Bypass using internal mammary artery
  - Bypass using saphenous vein

- **STENTING (PTCA OR PCI)**
Treatment

Pharmacologic Therapy
1-Guideline-directed medical therapy (GDMT) reduces the rates of death and MI similar to revascularization therapy.

2-Approaches to risk factor modification include the following recommendations:

- **Dyslipidemia:** Use moderate- or high-dose statin therapy in the absence of contraindications or adverse effects, in addition to lifestyle changes. Addition of ezetimibe (first) or a PCSK9 inhibitor (alirocumab and evolocumab) (second) is reasonable for patients who do not tolerate statins or do not attain a 50% decrease in LDL cholesterol (or LDL remains above 70–100 mg/dL).

- **Blood pressure:** If BP is ≥130/80 mm Hg, institute drug therapy in addition to or after a trial of lifestyle modifications.

- **Diabetes mellitus:** Pharmacotherapy to achieve a target A1C of ≤7% is reasonable for select patients (eg, short duration of diabetes and long life expectancy). An A1C goal of <8% is reasonable for other patients, such as those with micro- or macrovascular complications or coexisting medical conditions.

- **Annual influenza vaccinations** are recommended.

The PCSK9 gene provides instructions for making a protein that helps regulate the amount of cholesterol in the bloodstream.
Treatment

Pharmacologic Therapy

Antiplatelet Therapy

1- **Aspirin** reduced platelet activation and aggregation. A small percentage of patients are nonresponsive to aspirin's antiplatelet effects.

2- Anti-inflammatory drugs (**NSAIDs**) may interfere with aspirin's antiplatelet effect when coadministered by competing for the site of action in the **COX-1** enzyme.

3- The ACC/AHA guidelines contain the following recommendations for stable IHD:

   **Aspirin**: 75–162 mg daily should be continued.

   **Clopidogrel**: 75 mg daily is an appropriate alternative when aspirin is contraindicated.

4- Patient responsiveness to **clopidogrel is highly variable**, with estimates of nonresponsiveness ranging from 5% to 44% of patients. The most common cause of nonresponsiveness is **nonadherence**, but **genetic polymorphisms** to CYP2C19 may contribute in some patients.
Treatment

Pharmacologic Therapy

5-Some studies have suggested that patients receiving a **PPI** (most often omeprazole) together with clopidogrel have **reduced antiplatelet activity** and more ischemic events due to **inhibition** of cytochrome P450 enzymes involved in converting clopidogrel to its active metabolite. However, the only prospective randomized clinical trial conducted to date found **no increased rate of clinical events in patients given clopidogrel plus omeprazole**.

6-**Dual antiplatelet therapy** (DAPT) with aspirin plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is beneficial **after PCI with coronary stent placement** and **after treatment for ACS**. The combination of aspirin (75–162 mg daily) and clopidogrel 75 mg daily may be reasonable in **certain high-risk patients**.
Treatment

- Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

1. ACE inhibitors have not been shown to improve symptomatic ischemia or reduce chest pain episodes. Clinical trials of the role of ACE inhibitors or ARBs in reducing cardiovascular events (e.g., cardiovascular death, MI, stroke) in high-risk patients have produced conflicting results.

2. The ACC/AHA guidelines for stable IHD recommend the following strategies:
   - Use ACE inhibitors in patients who also have hypertension, diabetes, HFrEF, or chronic kidney disease, unless contraindicated.
   - ARBs are recommended for the same populations if patients are intolerant to ACE inhibitors.
   - Combination ACE inhibitor/ARB therapy should be avoided due to the lack of additional benefit and a higher risk of adverse events (e.g., hypotension, syncope, renal dysfunction).
Treatment

- **β-Adrenergic Blockers**
  1-β-Blockers competitively inhibit the effects of neuronally released and circulating catecholamines on β-adrenoceptors. Blockade of β1-receptors in the heart and kidney reduces HR, contractility, and BP, thereby decreasing MVO2.

  2-**β-Blockers are recommended over calcium channel blockers** (CCBs) for initial control of angina episodes in patients with stable IHD.

  3-The target is to lower the resting HR to 50–60 beats/min and the exercise HR to <100 beats/min. For patients (eg, elderly) who cannot tolerate these ranges, the target HR should be as low as can be tolerated above 50 beats/min.

  4-**β-Blockers may be combined** with CCBs or long-acting nitrates when initial treatment with β-blockers alone is unsuccessful.
**Treatment**

- **β-Adrenergic Blockers**

5- Only the β-blockers carvedilol, metoprolol succinate, and bisoprolol should be used in patients with HFrEF, starting with low doses and titrating upward slowly.

6- **β1-Selective** agents are preferred in patients with chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD), diabetes, dyslipidemia, and sexual dysfunction.

7- Drugs with combined α1- and β-blockade are effective for IHD, but agents with intrinsic sympathomimetic activity provide little to no reduction in resting HR and are not preferred except perhaps in patients with PAD or dyslipidemia.
Treatment

- **β-Adrenergic Blockers**

8-Common adverse effects include bradycardia, hypotension, heart block, impaired glucose metabolism, altered serum lipids (transiently increased triglycerides, decreased HDL-C, and no change in LDL-C), fatigue, depression, insomnia, and malaise.

9-**β-Blockers are contraindicated in patients with** preexisting bradycardia, hypotension, 2nd- or 3rd-degree atrioventricular (AV) block, uncontrolled asthma, severe PAD, hypotension, HFrEF with unstable fluid status, and diabetes associated with frequent episodes of hypoglycemia.

10-If β-blocker therapy must be discontinued, doses should be tapered over 2–3 weeks to prevent abrupt withdrawal, which can significantly increase in MVO2 and induce ischemia and even MI because of up-regulation of β-receptors in the myocardium.
Treatment

- **Calcium Channel Blockers**

1- All CCBs reduce MVO2 by reducing wall tension via lowering arterial BP and (to a minor extent) depressing contractility. CCBs also provide some increase in supply by inducing coronary vasodilation and preventing vasospasm.

2- **CCBs or long-acting nitrates** should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects.

3- **Dihydropyridine CCBs** (eg, nifedipine, amlodipine, isradipine, and felodipine) primarily affect vascular smooth muscle with little effect on the myocardium. These drugs produce minimal reduction in contractility and either no change or increased HR due to reflex tachycardia from direct arterial dilation. Nifedipine produces more impairment of LV function than amlodipine and felodipine.
Treatment

- **Calcium Channel Blockers**

4-Short-acting agents **should not** be used because of their greater propensity to cause *reflex tachycardia*. Other side effects of these CCBs include hypotension, headache, gingival hyperplasia, and peripheral edema.

5-Although most CCBs are **contraindicated** in patients with HFrEF, **amlodipine and felodipine** are considered **safe** options in these patients.

6-**Nondihydropyridine** CCBs (**verapamil** and **diltiazem**) mostly affect the myocardium with minimal effects on vascular smooth muscle; they reduce HR, contractility, and MVO2. Initial therapy for relief of symptoms with a long-acting nondihydropyridine **CCB instead of a β-blocker** is a reasonable approach.

7-**Common side effects of these CCBs include** bradycardia, hypotension, AV block, and symptoms of LV depression. These agents should be avoided in patients with concomitant HFrEF due to **negative inotropic effects**.
Treatment

- Calcium Channel Blockers

8-Verapamil may cause **constipation** in ~8% of patients. **Verapamil and diltiazem inhibit clearance of drugs** that utilize the cytochrome P450 3A4 isoenzyme such as carbamazepine, cyclosporine, lovastatin, simvastatin, and benzodiazepines.

9-Verapamil, and to a lesser extent diltiazem, also **inhibit P-glycoprotein–mediated drug transport**, which can increase concentrations of digoxin and cyclosporine. Verapamil also decreases digoxin clearance.

10-Agents that induce the 3A4 isoenzyme (phenobarbital, phenytoin, rifampicin) can reduce the effectiveness of all CCBs.
Treatment

Nitrates

1-Nitrates cause vasodilation. Most vasodilation occurs on the venous side, leading to reduced preload, myocardial wall tension, and MVO2.

2-Arterial vasodilation increases as doses are escalated, which can produce reflex tachycardia that can negate some of the antianginal benefits. This effect can be mitigated with concomitant β-blocker therapy.

3-All patients should have access to sublingual (SL) NTG 0.3 or 0.4 mg tablets or spray to treat acute angina episodes. Relief typically occurs within 5 minutes of administration.

4-SL nitrates can also be used to prevent acute episodes if given 2–5 minutes before activities known to produce angina; protection can last for up to 30 minutes with SL NTG and up to 1 hour with SL isosorbide dinitrate (ISDN).
Treatment

- **Nitrates**

5-Long-acting nitrates (or CCBs) should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects.

6-**Transdermal patches** and **isosorbide mononitrate** (ISMN) are most commonly prescribed for long-term prevention of angina episodes. ISDN is also effective, but the **three times daily regimen** requires dosing every 4–5 hours during the day to provide a nitrate-free interval.

7-Chronic nitrate use should incorporate a **10- to 14-hour nitrate-free interval each day to reduce nitrate tolerance**. Because this approach places the patient at risk for angina episodes, the **nitrate-free interval is usually provided during the nighttime hours** when the patient has a reduced MVO2 while sleeping.
Treatment

- **Nitrates**

8-The extended-release ISMN products that are dosed twice daily should be given 7 hours apart (eg, 7:00 AM and 2:00 PM). An extended-release, once daily ISMN product is available that provides 12 hours of nitrate exposure followed by a 12-hour nitrate-free interval.

9-Transdermal NTG patches are typically prescribed as “on in the AM and off in the PM” but patients should be given specific application and removal times (eg, apply at 8:00 AM and remove at 8:00 PM).

10-Nitrates should not be used routinely as monotherapy for stable IHD because of the lack of angina coverage during the nitrate-free interval, lack of protection against circadian rhythm (nocturnal) ischemic events, and potential for reflex tachycardia.
Treatment

- **Nitrates**

  11. **Concomitant β-blocker or diltiazem therapy** can prevent rebound ischemia during the nitrate-free interval.

  12. **Common nitrate side effects include** headache, flushing, nausea, postural hypotension, and syncope. **Headache can be treated with acetaminophen** and usually resolves after about 2 weeks of continued therapy.

  13. **Transdermal NTG may cause skin erythema and inflammation.** Initiating therapy with smaller doses and/or rotating the application site can minimize transdermal nitroglycerin side effects.
Treatment

- **Ranolazine**

1-Ranolazine reduces ischemic episodes by selective *inhibition of late sodium current* (INa), which reduces intracellular sodium concentration and improves myocardial *function and perfusion*.

2-It does **not** impact HR, BP, the inotropic state, or increase coronary blood flow. Ranolazine is effective as **monotherapy** for relief of angina symptoms but should only be used **if patients cannot tolerate traditional agents** due to hemodynamic or other adverse effects.

3-Because it does not substantially affect HR and BP, it is recommended as **add-on** therapy to traditional antianginal agents for **patients who achieve goal HR and BP and still have exertional angina symptoms**, **patients who cannot achieve these hemodynamic goals** due to adverse effects, and **patients who reach maximum doses of traditional agents but still have angina symptoms**.

4-It can be combined with a **β-blocker** when initial treatment with β-blockers alone is unsuccessful.
Treatment

- Ranolazine

5-Adverse effects include constipation, nausea, dizziness, and headache. Ranolazine can **prolong the QTc interval** and should be used with caution in patients receiving concomitant QTc-prolonging agents.

6-Potent **inhibitors** of CYP3A4 and P-glycoprotein (ketoconazole, itraconazole, protease inhibitors, clarithromycin, and nefazodone) or **potent inducers** of CYP3A4 and P-glycoprotein (phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin, rifapentine, St. John's wort) are **contraindicated with ranolazine** due to significant increases and decreases in ranolazine drug concentrations, respectively.

7-**Moderate CYP3A4 inhibitors** (eg, diltiazem, verapamil, erythromycin, and fluconazole) can be **used with ranolazine**, but the maximum dose **should not exceed 500 mg twice daily**.
Treatment

Treatment of Variable Threshold Angina and Prinzmetal Angina

1-Patients with variable threshold angina require pharmacotherapy for vasospasm. Most patients respond well to SL NTG for acute attacks.

2-Both CCBs and nitrates are effective for chronic therapy. CCBs may be preferred because they are dosed less frequently. Nifedipine, verapamil, and diltiazem are equally effective as single agents for initial management of coronary vasospasm; dose titration is important to maximize the response.

3-Patients unresponsive to CCBs alone may have nitrates added. β-Blockers are not useful for vasospasm because they may induce coronary vasoconstriction and prolong ischemia.
Treatment

- **Evaluation of therapeutic outcomes**

1-Assess for symptom improvement by **number of angina episodes**, weekly SL NTG use, and increased **exercise** capacity or duration of exertion needed to induce angina.

2-Use **statins** for dyslipidemia, strive to **achieve BP and A1C goals**, and implement the **lifestyle modifications of dietary modification, smoking cessation, weight loss, and regular exercise**.

3-Once patients have been optimized on medical therapy, symptoms should improve over **2–4 weeks** and remain stable until the disease progresses. Patients may require evaluation **every 1–2 months** until target endpoints are achieved; follow-up **every 6–12 months** thereafter is appropriate.
Treatment

- **Evaluation of therapeutic outcomes**

4-If the patient is doing well, no other assessment may be necessary. Although follow-up exercise tolerance testing with or without cardiac imaging can be performed to objectively assess control of ischemic episodes, this is rarely done if patients are doing well because of the expense involved.

5-Monitor for adverse drug effects such as headache and dizziness with nitrates; fatigue and lassitude with β-blockers; and peripheral edema, constipation, and dizziness with CCBs.

**Reference**
Anemia

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Anemia
Anemia is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood. The World Health Organization defines anemia as Hb less than 13 g/dL (130 g/L; 8.07 mmol/L) in men or less than 12 g/dL (120 g/L; 7.45 mmol/L) in women.
Classification

- **Morphologic** classifications are based on cell size. 1- **Macrocytic** cells are larger than normal 2- **Microcytic** cells are smaller than normal, 3- **normocytic** anemia may be associated with recent blood loss or chronic disease.

1. **Macrocytic** (Vitamin B12– and folic acid–deficiency anemias) can be caused by inadequate dietary intake, malabsorption syndromes, and inadequate utilization. Deficiency of intrinsic factor causes decreased absorption of vitamin B12 (ie, pernicious anemia). Folic acid–deficiency anemia can be caused by hyperutilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, longterm dialysis, or growth spurt. **Drugs** can cause anemia by reducing absorption of folate (eg, phenytoin) or through folate antagonism (eg, methotrexate).

2. **Microcytic** (Iron-deficiency anemia (IDA)), characterized by decreased levels of ferritin (most sensitive marker) and serum iron, and decreased transferrin saturation, can be caused by inadequate dietary intake, inadequate gastrointestinal (GI) absorption, increased iron demand (eg, pregnancy), blood loss, and chronic diseases.
Classification

3. **Anemia of inflammation** (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness associated with malignant, infectious, or inflammatory processes, tissue injury, and conditions associated with release of proinflammatory cytokines. Serum iron is decreased but in contrast to IDA, the serum ferritin concentration is normal or increased.

4. **Age-related** reductions in bone marrow reserve can render elderly patients more susceptible to anemia caused by multiple minor and often unrecognized diseases (eg, nutritional deficiencies) that negatively affect erythropoiesis.

5. **Pediatric** anemias are often due to a primary hematologic abnormality. The risk of IDA is increased by rapid growth spurts and dietary deficiency.
Each of the major categories of anemia (hypoproliferative, maturation disorders, and hemorrhage/hemolysis) can be further subclassified according to the functional defect in the several components of normal erythropoiesis.
# Diseases Causing Anemia of Inflammation

## Common causes
- Chronic infections
  - Tuberculosis
  - Other chronic lung infections (e.g., lung abscess, bronchiectasis)
  - Human immunodeficiency virus
  - Subacute bacterial endocarditis
  - Osteomyelitis
  - Chronic urinary tract infections
- Chronic inflammation
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Inflammatory bowel disease
  - Inflammatory osteoarthritis
  - Gout
  - Other (collagen vascular) diseases
  - Chronic inflammatory liver diseases

## Malignancies
- Carcinoma
- Lymphoma
- Leukemia
- Multiple myeloma

## Less common causes
- Alcoholic liver disease
- Congestive heart failure
- Thrombophlebitis
- Chronic obstructive pulmonary disease
- Ischemic heart disease
Clinical presentation

- Signs and symptoms depend on rate of development and age and cardiovascular status of the patient.

- Acute-onset anemia is characterized by *cardiorespiratory symptoms* such as palpitations, angina, orthostatic light-headedness, and breathlessness.

- Chronic anemia is characterized by *weakness, fatigue, headache, orthopnea, dyspnea* on exertion, vertigo, faintness, cold sensitivity, pallor, and loss of skin tone.

- IDA is characterized by *glossal pain, smooth tongue, reduced salivary flow*, pica (compulsive eating of nonfood items), and *pagophagia* (compulsive eating of ice).

- *Neurologic effects* (eg, numbness and paraesthesias) of vitamin B12 deficiency may precede hematologic changes. Psychiatric findings, including irritability, depression, and memory impairment, may also occur with vitamin B12 deficiency.

- Anemia with folate deficiency is **not** associated with neurologic symptoms.
Diagnosis

- Rapid diagnosis is essential because anemia is often a sign of underlying pathology.

- Severity of symptoms does not always correlate with the degree of anemia.

- Initial evaluation of anemia involves a complete blood cell count (CBC), reticulocyte index, and examination of the stool for occult blood.

- The earliest and most sensitive laboratory change for IDA is decreased serum ferritin (storage iron), which should be interpreted in conjunction with decreased transferrin saturation and increased total iron-binding capacity (TIBC). Hb, hematocrit (Hct), and RBC indices usually remain normal until later stages of IDA.
Diagnosis

- In **macrocytic** anemias, mean corpuscular volume is usually elevated to greater than 100.

- Vitamin B12 and folate conc. can be measured to differentiate between the two deficiency anemias. A vitamin B12 value less than 200 pg/mL (148 pmol/L) is diagnostic of vitamin B12–deficiency anemia.

- A decreased RBC folate concentration (less than 150 ng/mL) appears to be a better indicator of folate-deficiency anemia than a decreased serum folate concentration.

- The diagnosis of AI is usually one of exclusion, with consideration of coexisting iron and folate deficiencies. Serum iron is usually decreased, but, unlike IDA, serum ferritin is normal or increased, and TIBC is decreased.

- Elderly patients with symptoms of anemia should undergo a CBC with peripheral smear and reticulocyte count.

- **Pediatric** populations requires use of age- and sex-adjusted norms for laboratory values.
General algorithm for diagnosis of anemias

(MCV, mean corpuscular volume; TIBC, total iron-binding capacity; WBC, white blood cells.)
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 150–200 mg elemental iron in two or three divided doses.

  - Iron is best absorbed from meat, fish, and poultry.

  - Administer iron at least 1 hour before meals because food interferes with absorption, but administration with food may be needed to improve tolerability.

  - Consider parenteral iron for patients with iron malabsorption, intolerance of oral iron therapy, or nonadherence.

  - The following formula can be used to estimate the total dose of parenteral iron needed to correct anemia:

    \[
    \text{Dose of iron (mg)} = \text{whole blood hemoglobin deficit (g/dL)} \times \text{body weight (lb)} \quad \text{or} \\
    \text{Dose of iron (mg)} = \text{whole blood hemoglobin deficit (g/L)} \times \text{body weight (kg)} \times 0.22
    \]
Treatment

- An additional quantity of iron to replenish stores should be added (about **600 mg for women** and **1000 mg for men**).
- Iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol, and ferric carboxymaltose are available parenteral iron preparations with similar efficacy but **different molecular size**, pharmacokinetics, bioavailability, and adverse effect profiles.

<table>
<thead>
<tr>
<th>Iron Salt</th>
<th>Percent Elemental Iron</th>
<th>Common Formulations and Elemental Iron Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>20</td>
<td>60–65 mg/324–325 mg tablet, 60 mg/5 mL syrup, 44 mg/5 mL elixir, 15 mg/1 mL drops</td>
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<tr>
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<td>65 mg/200 mg tablet, 50 mg/160 mg tablet</td>
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<tr>
<td>Ferrous gluconate</td>
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</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
<td>66 mg/200 mg tablet, 106 mg/324–325 mg tablet</td>
</tr>
</tbody>
</table>
Treatment

- **Vitamin B12–Deficiency**

  ❖ Anemia Oral vitamin B12 supplementation is as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B12 absorption pathway is independent of intrinsic factor. **Initiate oral cobalamin at 1–2 mg daily for 1–2 weeks, followed by 1 mg daily.**

  ❖ Parenteral therapy acts more rapidly than oral therapy and is recommended if neurologic symptoms are present. A popular regimen is **IM cyanocobalamin, 1000 mcg daily for 1 week**, then weekly for 1 month, and then monthly for maintenance therapy. Initiate daily oral cobalamin administration after symptoms resolve.

  ❖ **Continue vitamin B12 for life** in patients with pernicious anemia.
Treatment

- **Folate-Deficiency Anemia**

  Oral folic acid, 1 mg daily for 4 months, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, a dose of 1–5 mg daily may be necessary. Parenteral folic acid is available but rarely necessary.
Treatment

- **Anemia of Inflammation**

  Treatment of AI is less specific than that of other anemias and should focus on correcting reversible causes. Reserve iron therapy for an established IDA; iron is not effective when inflammation is present. **RBC transfusions** are effective but should be limited to episodes of **inadequate oxygen transport** and Hb of 7–8 g/dL (70–80 g/L; 4.34–4.97 mmol/L).

  **Erythropoiesis-stimulating agents** (ESAs) can be considered, but response can be impaired in patients with AI. The initial dosage for **epoetin alfa** is 50–100 units/kg three times weekly and **darbepoetin alfa** 0.45 mcg/kg once weekly. Iron, cobalamin, and folic acid supplementation may improve response to ESA treatment.

  Potential toxicities of **exogenous ESA** administration include **increases in blood pressure**, nausea, headache, fever, bone pain, and fatigue. Hb must be monitored during ESA therapy. An increase in Hb greater than 12 g/dL (120 g/L; 7.45 mmol/L) with treatment or a rise of greater than 1 g/dL (10 g/L; 0.62 mmol/L) every 2 weeks has been associated with **increased mortality and cardiovascular events**.
Treatment

- Anemia in Pediatric Populations

  - Infants aged **9–12 months**: Administer **ferrous sulfate** 3–6 mg/kg/day (elemental iron) divided once or twice daily between meals for 4 **weeks**. Continue for two additional months in responders 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 folic acid is 1 mg.
Evaluation of therapeutic outcomes

- **IDA**: Positive response to oral iron therapy is characterized by modest reticulocytosis in a few days with an increase in **Hb seen at 2 weeks**. Reevaluate the patient if reticulocytosis does not occur. Hb should return to normal after **2 months**; continue iron therapy until iron stores are replenished and serum ferritin normalized (up to **12 months**).

- **Megaloblastic** anemia: Signs and symptoms usually improve within a few days after starting vitamin **B12 or folic acid therapy**. **Neurologic** symptoms can take longer to improve or can be irreversible, but should not progress during therapy. Reticulocytosis should occur within 3–5 days. Hb begins to rise a week after starting vitamin B12 therapy and should normalize in 1–2 months. Hct should rise within 2 weeks after starting folic acid therapy and should normalize within 2 months.
Evaluation of therapeutic outcomes

- **ESAs**: Reticulocytosis should occur within a few days. Monitor iron, TIBC, transferrin saturation, and ferritin levels at baseline and periodically during therapy. The optimal form and schedule of iron supplementation are unknown. Discontinue ESAs if a clinical response does not occur after 8 weeks.

- **Pediatrics**: Monitor Hb, Hct, and RBC indices 4–8 weeks after initiation of iron therapy. Monitor Hb or Hct weekly in premature infants.
Sickle Cell Disease

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Introduction

- Sickle cell syndromes, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are hereditary conditions characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs).
- **SCT** is the heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene producing HbS (HbAS) gene. Individuals with SCT are asymptomatic.
- **SCD** can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia (SCA), which now also includes HbSβ 0 -thal due to similarities in clinical severity. The heterozygous inheritance of HbS with another qualitative or quantitative β-globin mutation results in sickle cell hemoglobin C (HbSC), sickle cell β-thalassemia (HbSβ + -thal and HbSβ 0 -thal), and some other rare phenotypes.
Introduction

Sickle cell

Abnormal hemoglobin

Sickle cells blocking blood flow

Normal red blood cell

Normal hemoglobin
Pathophysiology

- Clinical manifestations of SCD are due to impaired circulation, RBC destruction, and stasis of blood flow and ongoing inflammatory responses.

- These changes result from disturbances in RBC polymerization and membrane damage. In addition to sickling, other factors contributing to the clinical manifestations include functional asplenia (and increased risk of infection by encapsulated organisms), deficient opsonization, and coagulation abnormalities. 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, leading to local tissue hypoxia that accentuates 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, resulting in shortened circulatory survival and chronic hemolysis.
Clinical presentation

- SCD involves multiple organ systems. Clinical manifestations depend on the genotype (Table 1).

- Cardinal features of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4–6 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.

- Acute complications of SCD include fever and infection (eg, sepsis caused by encapsulated pathogens such as Streptococcus pneumoniae), stroke, acute chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
Clinical presentation

- **Chronic** complications involve many **organs** and include pulmonary hypertension, airway inflammation and hyperresponsiveness, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, depression, hematuria, and other renal complications. Children experience delayed growth and sexual maturation.

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell trait (SCT)</td>
<td>Rare painless hematuria; heavy exercise under extreme conditions can provoke gross hematuria and complications (normal Hb)</td>
</tr>
<tr>
<td>Sickle cell anemia (SCA-HbSS)</td>
<td>Pain episodes, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstones, priapism, leg ulcers; anemia (Hb 6–9 g/dL [60–90 g/L; 3.72–5.59 mmol/L])</td>
</tr>
<tr>
<td>Sickle cell hemoglobin C (HbSC)</td>
<td>Painless hematuria and rare aseptic necrosis of bone; pain episodes are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 9–14 g/dL [90–140 g/L; 5.59–8.69 mmol/L])</td>
</tr>
<tr>
<td>Sickle cell β⁺-thalassemia (HbSβ⁺-thal)</td>
<td>Rare pain; milder severity than HbSS because production of some HbA; Hb 9–12 g/dL (90–120 g/L; 5.59–7.45 mmol/L) with microcytosis</td>
</tr>
<tr>
<td>Sickle cell β₀-thalassemia (HbSβ₀-thal)</td>
<td>No HbA production; severity similar to SCA; Hb 7–9 g/dL (70–90 g/L; 4.34–5.59 mmol/L) with microcytosis</td>
</tr>
</tbody>
</table>
Diagnosis

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing, high-performance liquid chromatography (HPLC), or electrophoresis.
- Laboratory findings include low hemoglobin; increased reticulocyte, platelet, and white blood cell counts; and sickled red cell forms on the peripheral smear.
Treatment

- Goals of Treatment: The goals are to reduce hospitalizations, complications, and mortality.

- Patients with SCD require lifelong interprofessional care that combines general symptomatic supportive care, preventative medical therapies, and specific disease-modifying therapies.

- Routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations are recommended.

- Prophylactic penicillin is recommended until at least 5 years of age. An effective regimen is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg orally twice daily until age 5 years.
Disease-Modifying Therapies

- HbF directly affects polymer formation. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent pain and higher mortality.

- HbF levels of 20% or greater reduce the risk of acute sickle cell complications.

- Hydroxyurea, a chemotherapeutic agent, stimulates HbF production and increases the number of HbF-containing reticulocytes and intracellular HbF. It is indicated for patients 2 years of age and older with recurrent moderate to severe painful crises to reduce the frequency of pain crises and the need for blood transfusions.

- The recommended single daily dose for adults is 15 mg/kg and 20 mg/kg for children.
Disease-Modifying Therapies

- **L-Glutamine** is approved for SCD patients age 5 and older to reduce the acute complications of SCD. Dose is **weight-based**: 5 g twice a day for 65 kg.

- Chronic **RBC transfusions** are indicated for primary and secondary stroke prevention and amelioration of organ damage. Transfusions are usually given every 3–4 weeks or as needed to maintain desired HbS levels.

- **Allogeneic hematopoietic stem cell transplantation** is the only **curative** therapy for SCD. The best candidates are **younger than 16 years**, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include **mortality, graft rejection, and secondary malignancies**.
Hydroxyurea

Adults and children with SCD in whom hydroxyurea is indicated

Baseline laboratory: CBC, reticulocyte, HbF, chemistries (including creatinine, bilirubin, ALT), pregnancy test (if menstruating)
Baseline physical examination and history

* Pregnancy test negative
* Use contraception for sexually active men and women
* Adherence with daily dosing, frequent laboratory monitoring, and medical appointments

No hydroxyurea

Hydroxyurea: 15 mg/kg/day for adults and 20 mg/kg/day for children. May increase by 5 mg/kg/day every 8 weeks up to 35 mg/kg/day

Monitoring:
* CBC: every 4 weeks until maximum tolerated dose achieved for 8-12 wks, then every 8 weeks
* HbF every 3 months × 2 than every 6 months
* Bilirubin, ALT, and creatinine every 12-24 weeks
* Pregnancy test PRN (if positive, stop therapy and provide teratogen risk counseling)
* History and PE: every 4 weeks until maximum dose achieved for 8-12 weeks, then every 8 weeks

(ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSSβ 0, sickle cell β 0-thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.)
Hydroxyurea

Treatment Goals:
- Less pain and ACS episodes
- ↑ HbF
- ↑ Hgb (if severe anemic)
- Improved well-being
- Acceptable myelotoxicity

No response in more than 3-6 months

Yes

Continue therapy
Continue monitoring

Toxicity develops

Assess compliance if no ↑ MCV or HbF
Consider inability to respond to therapy
- Cautiously increase dose up to 35 mg/kg/day. Trial period of 6-12 months is probably adequate

Toxicity:
- ANC <2,000 cells/mm³
- Platelets <80,000 cells/mm³
- Absolute reticulocyte count <80,000 cells/mm³ if Hgb <9 g/dL
- Hgb <5 g/dL or >20% below baseline
- Increased serum creatinine 50% above baseline
- Increased ALT 100% above baseline

Stop hydroxyurea for at least 1 week and until toxicity resolves

Resume hydroxyurea at 2.5-5 mg/kg/day less than previous dose
May resume previous dose if no toxicity recurs after 12 weeks of the lower dose
- If toxicity recurs on higher dose, stop hydroxyurea again until resolves, then resume at the lowest tolerated dose

(ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSSβ0, sickle cell β0-thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.)
Treatment of Complications

- Educate patients to recognize conditions that require **urgent** evaluation. **Balanced fluid status and oxygen saturation of at least 92%** are important to avoid exacerbation during acute illness.

- **RBC transfusions** are indicated for **acute exacerbation** of baseline anemia (eg, aplastic crisis, hepatic or splenic sequestration, or severe hemolysis), severe vasoocclusive episodes, and procedures requiring general anesthesia.

- Promptly evaluate fever of **38.5°C (101.3°F)** or higher. Empiric antibiotic therapy should provide coverage against encapsulated organisms (eg, ceftriaxone for outpatients and cefotaxime for inpatients; clindamycin for cephalosporin-allergic patients).

- For acute chest syndrome (ACS), initiate incentive **spirometry**; appropriate fluid therapy; broad-spectrum antibiotics, including a **macrolide or quinolone**; and, for hypoxia or acute distress, **oxygen** therapy. Other potential therapies include **steroids and nitric oxide**.
Treatment of Complications

- **Priapism** has been treated with analgesics, antianxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (eg, phenylephrine and epinephrine), and vasodilators to relax smooth muscle (eg, terbutaline and hydralazine).

- Treatment of **aplastic crisis** is primarily supportive. **Blood transfusions** may be indicated for severe or symptomatic anemia.

- **Hydration** and blood transfusions are indicated to treat **hypovolemia** associated with splenic sequestration. Manage recurrent episodes with observation and splenectomy. Consider chronic transfusions in children younger than 2 years of age to delay splenectomy until the age of 2 years. Splenectomy is an option for chronic hypersplenism.

- **Hydration and analgesics** are mainstays of treatment for **vasoocclusive** (painful) crisis. Administer fluids IV or orally at 1–1.5 times the maintenance requirement; monitor closely to avoid volume overload. Consider an infectious etiology and initiate empiric therapy if indicated.
Treatment of Complications

- Tailor analgesic therapy to the individual because of the variable frequency and severity of pain. Pain scales should be used to quantify the degree of pain.

- Use nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for mild to moderate pain. Consider adding an opioid if mild to moderate pain persists. (e.g., codeine or hydrocodone).

- Treat severe pain aggressively with an opioid, such as morphine, hydromorphone, fentanyl, or methadone. Avoid meperidine due to accumulation of the normeperidine metabolite, which can cause neurotoxicity, especially in patients with impaired renal function.

- Treat severe pain 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.

- Treatment of chronic pain in SCD requires an interprofessional team approach. Guidelines for chronic pain management are available.
Evaluation of therapeutic outcomes

- Evaluate patients on a regular basis to establish baseline symptoms, monitor changes, and provide age-appropriate education.

- Evaluate CBC and reticulocyte counts every 3–6 months up to 2 years of age, then every 6–12 months.

- Screen HbF level annually until 2 years of age. Evaluate renal, hepatobiliary, and pulmonary function annually.

- Screen patients for retinopathy. Assess efficacy of hydroxyurea by monitoring the number, severity, and duration of sickle cell crises.
TQ
Heart Failure

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ISPOR, ISOP member, ICIT
Introduction

1-Heart failure (HF) is a progressive syndrome that can result from any changes in cardiac structure or function that impair the ability of the ventricle to fill with or eject blood.

2-HF may be caused by an abnormality in systolic function, diastolic function, or both.

3-HF with reduced systolic function (ie, reduced left ventricular ejection fraction, LVEF) is referred to as HF with reduced ejection fraction (HFrEF).

4-Preserved LV systolic function (ie, normal LVEF) with presumed diastolic dysfunction is termed HF with preserved ejection fraction (HFpEF).
**Introduction**

In HF with reduced ejection fraction (HFrEF), the left ventricle fills with blood but is only able to pump up to 40% of its volume before refilling.

In HF with preserved ejection fraction (HFP EF), the left ventricle has stiff and often thick walls and can therefore fill with only a small amount of blood, so even if it pumps all of its volume it is not enough to meet the body’s needs.
Pathophysiology

1-Causes of systolic dysfunction (decreased contractility) include reduced muscle mass (eg, myocardial infarction [MI]), dilated cardiomyopathies, and ventricular hypertrophy. Ventricular hypertrophy can be caused by pressure overload (eg, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or volume overload (eg, valvular regurgitation).

2-Causes of diastolic dysfunction (restriction in ventricular filling) include increased ventricular stiffness, ventricular hypertrophy, infiltrative myocardial diseases, myocardial ischemia and MI, mitral or tricuspid valve stenosis, and pericardial disease (eg, pericarditis and pericardial tamponade).
Pathophysiology

3-The leading causes of HF are coronary artery disease and hypertension.

4-Decreased cardiac output (CO) results in activation of compensatory responses to maintain circulation:

(A) Tachycardia and increased contractility through sympathetic nervous system activation, (B) The Frank–Starling mechanism, whereby increased preload (through sodium and water retention) increases stroke volume, (C) vasoconstriction, and (D) ventricular hypertrophy and remodeling.

5-Although these compensatory mechanisms initially maintain cardiac function, they are responsible for the symptoms of HF and contribute to disease progression.
Pathophysiology

6-Chronic activation of the neurohormonal systems [angiotensin II, norepinephrine, aldosterone, natriuretic peptides, arginine vasopressin (AVP)] results in a cascade of events that affect the myocardium.

7-These events lead to changes in ventricular size (left ventricular hypertrophy), shape, structure, and function known as ventricular remodeling.

8-The alterations in ventricular function result in further deterioration in cardiac systolic and diastolic functions that further promotes the remodeling process.

9-Common precipitating factors that may cause a previously compensated HF patient to decompensate include myocardial ischemia and MI, pulmonary infections, nonadherence with diet or drug therapy, and inappropriate medication use.

10-Drugs may precipitate or exacerbate HF through negative inotropic effects, direct cardiotoxicity, or increased sodium and water retention.
Pathophysiology

Heart Failure (HF): Pathophysiology

- The inability of the heart to provide sufficient output to meet the demands of the body
- A variety of disorders can lead to low output or high output failure
- Pulmonary and systemic venous congestion
- Increased sympathetic nervous system activity
- ADH secretion from the brain
- Increased preload
- Cardiac dilation and hypertrophy
- Increased afterload
- Neuro-hormonal responses worsen HF
- We need blood flow! Try harder!
- Help...
- We're getting backed up. Do your job!
- Put a cork in it. We're releasing hormones.

Notes:
- Increased sympathetic nervous system activity leads to increased neuro-hormonal responses which worsen heart failure.
Clinical presentation

1-Patient presentation may range from asymptomatic to cardiogenic shock. **Primary symptoms are dyspnea** (especially on exertion) and fatigue, which lead to exercise intolerance.

2-Other **pulmonary symptoms include**: orthopnea, paroxysmal nocturnal dyspnea (PND), tachypnea, and cough. Fluid overload can result in pulmonary congestion and peripheral edema.

3-**Nonspecific symptoms may include** fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite or early satiety, and weight gain or loss.

4-**Physical examination may reveal** pulmonary crackles, cool extremities, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness and anxiety, sometimes with coughing and pink, frothy sputum), peripheral edema, jugular venous distention (JVD), hepatomegaly, and mental status changes.
Clinical presentation

Do you know the symptoms of HF?

Shortness of Breath
Chronic Coughing or Wheezing
Build-up of Fluid (edema)
Fatigue or Feeling Lightheaded
Nausea or Lack of Appetite
Confusion or Impaired Thinking
High Heart Rate

People who experience more than one should be evaluated.
**Diagnosis**

1- A complete **history and physical examination** with appropriate laboratory testing are essential in evaluating patients with suspected HF.

2- **Laboratory tests** for identifying disorders that may cause or worsen HF include CBC; serum **electrolytes** (including calcium and magnesium); renal, hepatic, thyroid function tests, and iron studies; urinalysis; lipid profile; and A1C. **Hyponatremia** may indicate worsening volume overload and/or disease progression and is associated with reduced survival.

3- **Serum creatinine** may be increased due to hypoperfusion; preexisting renal dysfunction can contribute to volume overload. **B-type natriuretic peptide (BNP)** and NT-proBNP are increased.

4- **Ventricular hypertrophy** can be demonstrated on chest **radiograph** or **electrocardiogram (ECG)**. Chest radiograph may also show pleural effusions or pulmonary **edema**.
Diagnosis

5- **Echocardiogram** can identify abnormalities of the pericardium, myocardium, or heart valves and quantify LVEF to determine if **systolic or diastolic** dysfunction is present.

6-The **New York Heart Association Functional Classification System** is intended primarily to classify symptoms according to the physician’s subjective evaluation.

I. **Functional class (FC)-I** patients have **no limitation** of physical activity.
II. **FC-II** patients have **slight** limitation.
III. **FC-III** patients have **marked** limitation
IV. **FC-IV** patients are **unable to carry on** physical activity without discomfort.

7-The American College of Cardiology/American Heart Association (**ACC/AHA**) staging system provides (**Stages A, B, C, and D**) a more comprehensive framework for evaluating, preventing, and treating HF.
Goals of Treatment: Improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.

General Approach

The first step is to determine the etiology or precipitating factors. Treatment of underlying disorders (eg, hyperthyroidism) may avoid the need for treating HF.
Treatment of chronic heart failure

ACC/AHA Stage A:

1-These are patients at high risk for developing HF. Identify and modify risk factors to prevent development of structural heart disease and subsequent HF.

2-Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia.

3-Although treatment must be individualized, ACE inhibitors or ARBs are recommended for HF prevention in patients with multiple vascular risk factors.
Treatment of chronic heart failure

ACC/AHA Stage B:

1-These patients have structural heart disease but no HF signs or symptoms. Treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process.

2-In addition to treatment measures outlined for stage A, patients with reduced LVEF (<40%) should receive an ACE inhibitor (or ARB) and β-blocker to prevent development of HF, regardless of whether they have had an MI.

3-Patients with a previous MI and reduced LVEF should also receive an ACE inhibitor or ARB, β-blockers, and a statin.
Treatment of chronic heart failure

ACC/AHA Stage C:
1-These patients have structural heart disease and previous or current HF symptoms and include both HFrEF and HFpEF.

2-In addition to treatments for stages A and B, patients with HFrEF in stage C should receive guideline-directed medical therapy (GDMT) that includes an ACE inhibitor, ARB, or angiotensin receptor–neprilysin inhibitor (ARNI; valsartan–sacubitril) together with an β-blocker, and an aldosterone antagonist in eligible patients to reduce morbidity and mortality.

3-Loop diuretics, hydralazine–isosorbide dinitrate (ISDN), digoxin, and ivabradine are also used in select patients.
Treatment of chronic heart failure

ACC/AHA Stage D HFrEF:

1-These patients have persistent HF symptoms despite maximally tolerated GDMT.

2-They should be considered for specialized interventions, including mechanical circulatory support, continuous IV positive inotropic therapy, cardiac transplantation, or hospice care (when no additional treatments are appropriate).
Treatment of chronic heart failure

Nonpharmacologic Therapy of Chronic Heart Failure

1-Interventions include restriction of fluid intake and dietary sodium intake (<2–3 g of sodium/day) with daily weight measurements.

2-In patients with hyponatremia or persistent volume retention despite high diuretic doses and sodium restriction, limit daily fluid intake to 2 L/day from all sources.

3-Revascularization or anti-ischemic therapy in patients with coronary disease may reduce HF symptoms. Drugs that can aggravate HF should be discontinued if possible.
Pharmacologic Therapy for Stage C HFrEF

A-Diuretics

1-Diuretic therapy (in addition to sodium restriction) is recommended for all patients with clinical evidence of fluid retention.

2-However, because they do not alter disease progression or prolong survival, diuretics are not required for patients without fluid retention.

3-Thiazide diuretics (eg, hydrochlorothiazide) are relatively weak and are infrequently used alone in HF. However, thiazides or the thiazide-like diuretic metolazone can be used in combination with a loop diuretic to promote very effective diuresis.
Treatment of chronic heart failure

4-Thiazides may be preferred over loop diuretics in patients with only mild fluid retention and elevated BP because of their more persistent antihypertensive effects.

5-Loop diuretics (furosemide, bumetanide, and torsemide) are usually necessary to restore and maintain euvolemia in HF.

6-Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.

7-Adverse effects of diuretics include hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, and renal dysfunction.
Treatment of chronic heart failure

**Angiotensin-Converting Enzyme Inhibitors**

1-ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HFrEF.

2-Current guidelines recommend that all patients with HFrEF, regardless of whether or not symptoms are present, should receive an ACE inhibitor to reduce morbidity and mortality, unless there are contraindications.

3-The benefits of ACE inhibitors are independent of HF etiology (ischemic vs nonischemic) and are greatest in patients with the most severe symptoms.

4-Start therapy with low doses followed by gradual titration as tolerated to the target or maximally tolerated doses. Dose titration is usually accomplished by doubling the dose every 2 weeks.

5-Evaluate blood pressure (BP), renal function, and serum potassium at baseline and within 1–2 weeks after the start of therapy and after each dose increase.
Treatment of chronic heart failure

6-Although symptoms may improve within a few days of starting therapy, **it may take weeks to months before the full benefits are apparent.** Even if symptoms do not improve, continue long-term therapy to reduce mortality and hospitalizations.

7-**The most common adverse effects include** hypotension, renal dysfunction, and hyperkalemia. A dry, nonproductive cough (occurring in **15%–20%** of patients) is the most common reason for discontinuation.

8-Because cough is a bradykinin-mediated effect, replacement with an **ARB** is reasonable; however, caution is required because **cross-reactivity** has been reported.

9-**Angioedema** occurs in approximately **1%** of patients and **is potentially life threatening**; ACE inhibitors are **contraindicated** in patients with a history of angioedema.

10-ACE inhibitors are **contraindicated in pregnancy** due to various congenital defects.
Treatment of chronic heart failure

C-Angiotensin Receptor Blockers

1-Because ARBs do not affect bradykinin, they are not associated with cough and have a lower risk of angioedema than ACE inhibitors.

2-ARBs are now recommended as an alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema.

3-Although numerous ARBs are available, only candesartan, valsartan, and losartan are recommended in the guidelines because efficacy has been demonstrated in clinical trials.

4-As with ACE inhibitors, initiate therapy with low doses and then titrate to target doses. Evaluate BP, renal function, and serum potassium within 1–2 weeks after starting therapy and after dosage increases, with these parameters used to guide subsequent dose changes.
Treatment of chronic heart failure

5-ARBS are **not suitable alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors** because they are just as likely to cause these adverse effects.

6-**Careful monitoring** is required when an ARB is used with another inhibitor of the renin-angiotensin aldosterone (RAAS) system (eg, ACE inhibitor or aldosterone antagonist) because this combination increases the risk of these adverse effects.

7-**Caution** should be exercised when ARBs are used in patients with **angioedema from ACE inhibitors** because **cross-reactivity** has been reported. Similar to ACE inhibitors, ARBs are contraindicated in pregnancy.
Treatment of chronic heart failure

D-Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

1-Valsartan/Sacubitril is an ARNI approved to reduce the risk of cardiovascular death and hospitalization for HF in patients with NYHA class II–IV HF and reduced LVEF.
Treatment of chronic heart failure

2-Neprilysin is an enzyme that degrades bradykinin and other endogenous vasodilator and natriuretic peptides. By reducing neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced, and renin and aldosterone secretion is inhibited.

3-In patients with HFrEF and NYHA class II–III symptoms tolerating an ACE inhibitor or ARB, current guidelines recommend replacing those drugs with the ARNI to further reduce morbidity and mortality.
Treatment of chronic heart failure

4-Discontinue ACE inhibitors 36 hours prior to initiating the ARNI; no waiting period is needed in patients receiving an ARB. Titrate the initial starting dose to the target dose after 2–4 weeks.

5-Closely monitor BP, serum potassium, and renal function after the start of therapy and after each titration step.

6-The most common adverse effects include hypotension, dizziness, hyperkalemia, worsening renal function, and cough. Angioedema is most common with sacubitril/valsartan than with enalapril.

7-Sacubitril/valsartan is contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB. It is also contraindicated in pregnancy and should not be used concurrently with ACE inhibitors or other ARBs.
**Treatment of chronic heart failure**

**E-β-Blockers**

1-β-Blockers antagonize the effects of the sympathetic nervous systems in HF and slow disease progression. β-blockers **reduce HF mortality, and hospitalizations**.

2-The ACC/AHA guidelines **recommend** use of β-blockers in **all stable patients** with HFrEF in the absence of contraindications or a clear history of β-blocker intolerance.

3-Patients **should** receive a β-blocker **even if symptoms are mild or well controlled** with ACE inhibitor and diuretic therapy.

4-β-Blockers are also recommended for asymptomatic persons with a reduced LVEF (stage B) to decrease the risk of progression to HF.

5-**Carvedilol, metoprolol succinate (CR/XL), and bisoprolol** are the only β-blockers shown to reduce mortality in large HF trials.
Treatment of chronic heart failure

6-Initiate β-blockers in **stable patients** who have **no or minimal** evidence of fluid overload. Because of their **negative inotropic effects**, start β-blockers in **very low doses** with slow upward **dose titration** to avoid symptomatic worsening or acute decompensation. Doses should be doubled no more often than **every 2 weeks**, as tolerated, until the target or maximally tolerated dose is reached.

7-**Inform patients that** β-blocker therapy is expected to **positively** influence disease progression and survival **even if there is little symptomatic improvement**. In addition, **dose titration is a long, gradual process**; **response to therapy may be delayed**; and **HF symptoms may actually worsen during the initiation period**.

8-**Adverse effects include** bradycardia, hypotension, fatigue, impaired glycemic control, bronchospasm in patients with asthma, and worsening HF.

9-**Absolute contraindications include** uncontrolled bronchospastic disease, symptomatic bradycardia, advanced heart block without a pacemaker, and acute decompensated HF. However, β-blockers may be tried with caution in patients with asymptomatic bradycardia, COPD, or well-controlled asthma.
Treatment of chronic heart failure

F-Aldosterone Antagonists

1- **Spironolactone** and **eplerenone** block mineralocorticoid receptors, the target for aldosterone. [In the kidney, inhibit sodium reabsorption and potassium excretion, In the heart, decrease cardiac fibrosis and ventricular remodeling]. Aldosterone antagonists also decrease the proinflammatory state, atherogenesis, and oxidative stress caused by aldosterone.

2- Current guidelines recommend **adding a low-dose aldosterone antagonist** to standard therapy to **improve** symptoms, reduce the risk of HF hospitalization, and **increase survival in select patients** provided that serum potassium and renal function can be carefully monitored.
Treatment of chronic heart failure

3-Low-dose aldosterone antagonists may be appropriate for:
(A) patients with mild to moderately severe HFrEF (NYHA class II–IV) who are receiving standard therapy, and (B) those with LV dysfunction and either acute HF or diabetes early after MI.

4-Start with low doses. **Avoid** aldosterone antagonists in patients with renal impairment, elevated serum potassium, or history of severe hyperkalemia.

5-Spirofolactone also interacts with androgen and progesterone receptors, which may lead to **gynecomastia, impotence**, and **menstrual irregularities** in some patients.
G-Nitrates and Hydralazine

1-Isosorbide dinitrate (ISDN) is a venodilator that reduces preload, whereas hydralazine is a direct arterial vasodilator that reduces systemic vascular resistance (SVR) and increases stroke volume and CO.

2-Guidelines recommend addition of hydralazine/ISDN to African Americans with HFrEF and NYHA class III–IV symptoms treated with ACE inhibitors (or ARBs) and β-blockers.

3-The combination can also be useful in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or hypotension.

4-Obstacles to successful therapy with the combination include the need for frequent dosing (ie, three times daily with the fixed-dose combination product), high frequency of adverse effects (eg, headache, dizziness, and GI distress), and increased cost for the fixed-dose combination product.
Treatment of chronic heart failure

H-Ivabradine

1-Ivabradine inhibits the If current (Funny current pacemaker) in the sinoatrial node that is responsible for controlling HR, thereby slowing the HR. It does not affect AV conduction, BP, or myocardial contractility.

2-Because of the clear benefits of β-blockers on mortality, clinicians should titrate to the maximum tolerated doses before considering use of ivabradine.

3-Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in patients with LVEF ≤35% who are in sinus rhythm with resting HR ≥70 bpm and are either on a maximally tolerated dose of a β-blocker or have a contraindication to β-blocker use.

4-The most common adverse effects are bradycardia, atrial fibrillation, and visual disturbances.
Treatment of chronic heart failure

I-Digoxin

1-Although digoxin has **positive inotropic effects**, its benefits in HF are related to its neurohormonal effects. It attenuates the excessive sympathetic nervous system activation in HF and increases parasympathetic activity, thereby decreasing HR and enhancing diastolic filling.

2-Studies of digoxin in HF showed either neutral effects or reductions in hospitalizations and either neutral or detrimental effects of digoxin on mortality.

3-So digoxin is **not considered a first-line agent in HF**, but a trial may be considered in conjunction with GDMT including ACE inhibitors (or ARBs), β-blockers, and diuretics in patients with symptomatic HFrEF to **improve symptoms and reduce hospitalizations**.
Treatment of chronic heart failure

4-Digoxin may also be considered to help control ventricular rate in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective rate control agents, especially during exercise.

5-In the absence of digoxin toxicity or serious adverse effects, digoxin should be continued in most patients. Digoxin withdrawal may be considered for asymptomatic patients who have significant improvement in systolic function with optimal ACE inhibitor and β-blocker treatment.
Treatment of chronic heart failure

**Pharmacologic Therapy for HFpEF**

1-Many of the drugs are the same as those used to treat HFrEF (eg, diuretics, β-blockers), but the rationale and dosing may be different.

2-A loop or a thiazide diuretic should be considered for patients with volume overload. Use a loop diuretic for more severe volume overload or inadequate response to a thiazide.

3-Avoid lowering preload excessively, which may reduce stroke volume and CO. Start diuretics at low doses to avoid hypotension and fatigue.

4-ACE inhibitors may be considered in all patients, especially patients with symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.
Treatment of chronic heart failure

**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

\[ \uparrow \text{Afterload} = \uparrow \text{Cardiac workload} \]
Treatment of chronic heart failure

5-**ARBs may be considered in all patients,** especially those who are intolerant of ACE inhibitors.

6-**Aldosterone antagonists** can reduce the risk of hospitalization in patients who do not have contraindications and are not at risk for hyperkalemia. They may be beneficial for patients with elevated BNP or NT-proBNP.

7-**β-Blockers should be considered in patients with one or more of the following conditions:** (1) MI, (2) hypertension, and (3) atrial fibrillation requiring ventricular rate control.

8-**Nondihydropyridine calcium channel blockers** (CCB; diltiazem or verapamil) should be considered for patients with atrial fibrillation warranting ventricular rate control who either are intolerant to or have not responded to a β-blocker.

9-**A nondihydropyridine or dihydropyridine** (eg, amlodipine) CCB can be considered for symptom-limiting angina or hypertension.