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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).

Classification	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

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 $\geq 140/90$ mm Hg.

C-For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or an elevated 10-year ASCVD risk $\geq 10\%$, **the threshold for starting drug therapy is $\geq 130/80$ 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

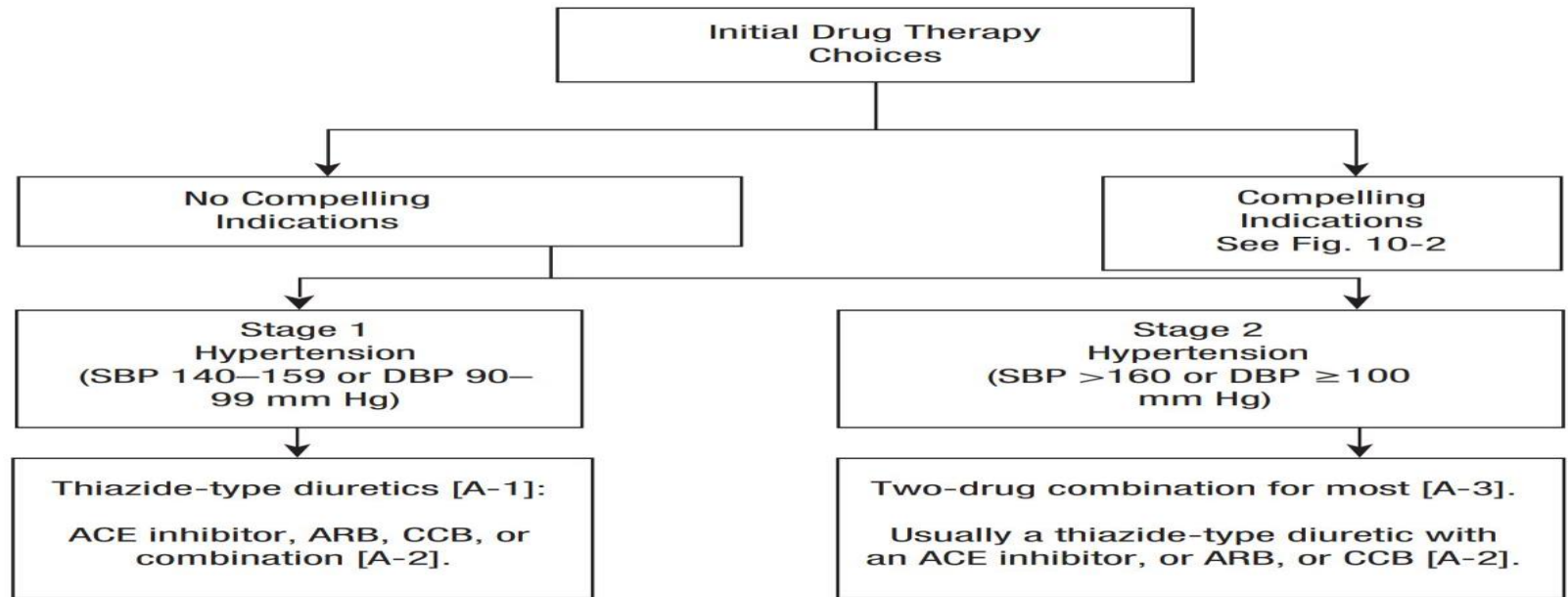
4-The **four first-line options** are angiotensin-converting enzyme (**ACE**) inhibitors, angiotensin II receptor blockers (**ARBs**), calcium channel blockers (**CCBs**), and **thiazide diuretics**.

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 (α 1-blockers, direct renin inhibitors, central α 2-agonists, and direct arterial vasodilators) may be used for select patients **after implementing first-line agents**.



Pharmacologic Therapy



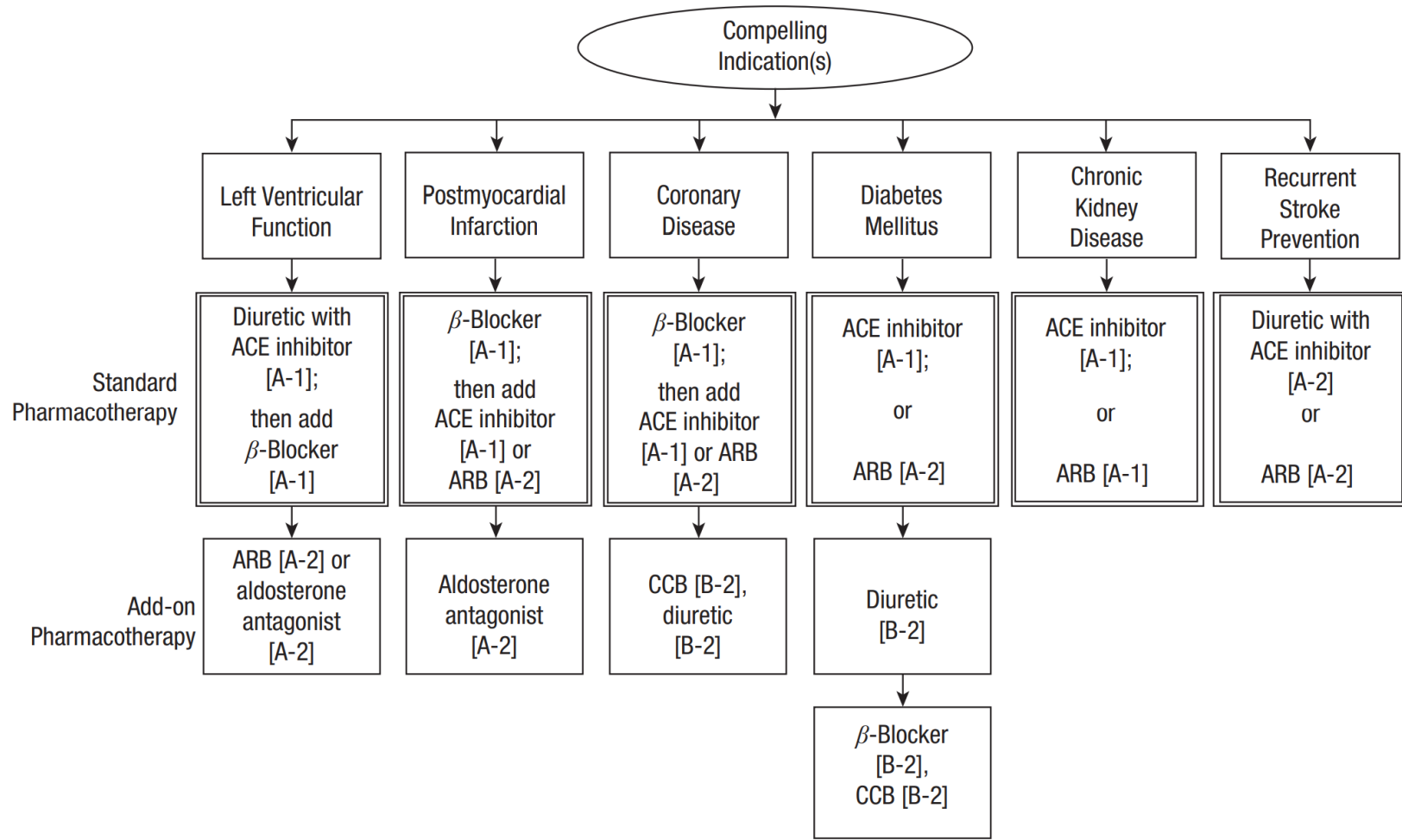
Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled trial. 2 = Evidence from at least one well-designed clinical trial with randomization; from cohort or 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



A-Heart Failure with *Reduced Ejection Fraction* (HFrEF)

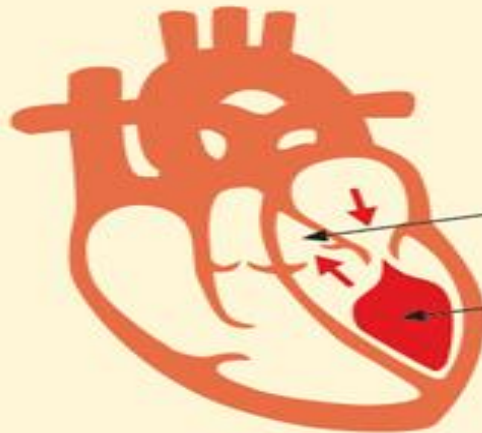
- ▶ Heart failure is a clinical syndrome characterized by dyspnea or exertional limitation due to impairment of **ventricular filling or ejection of blood or both**.
- ▶ HF has increased to an estimated **23 million** people, and approximately **50%** of cases are HF with reduced ejection fraction
- ▶ 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:

$$\frac{\text{AMOUNT OF BLOOD PUMPED OUT}}{\text{AMOUNT OF BLOOD IN THE CHAMBER}} =$$

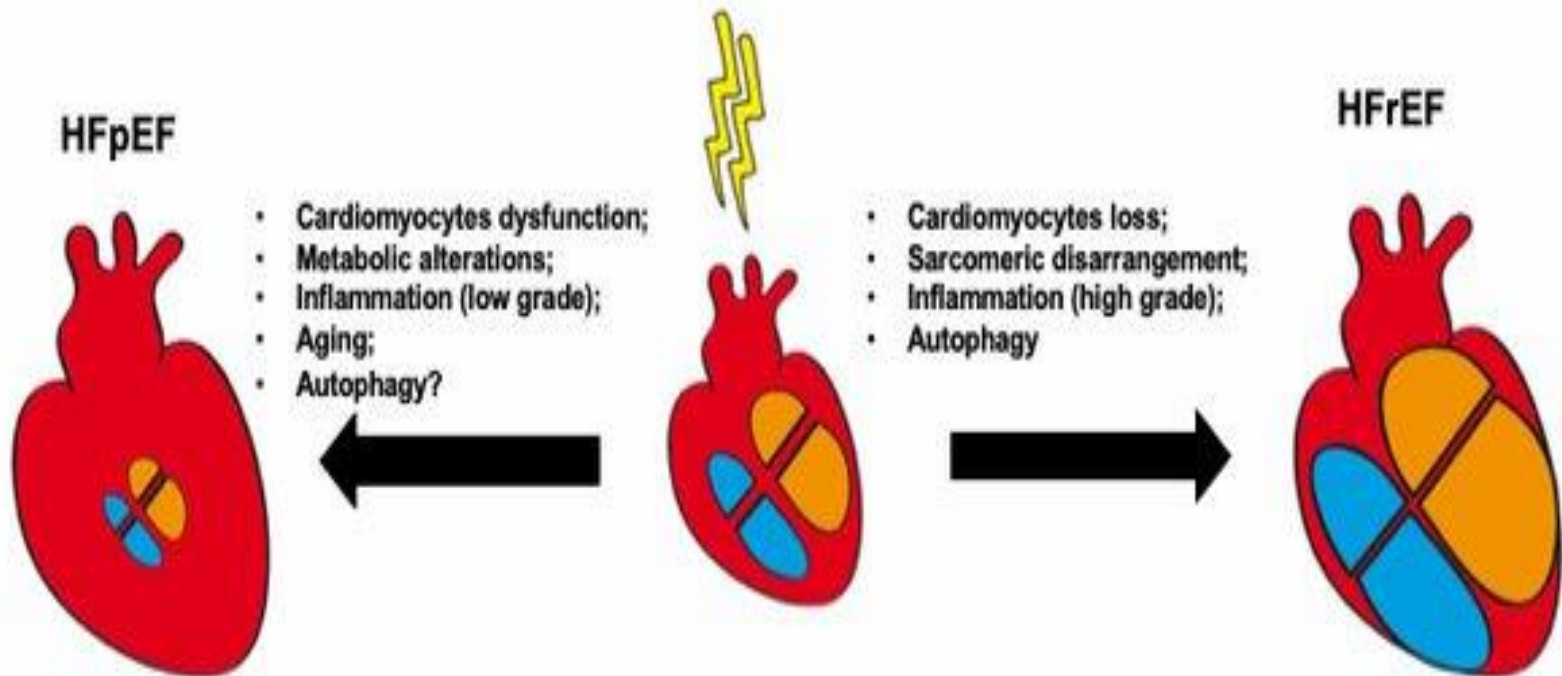
%
(EF)

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
≤ 40%
IS PUMPED OUT AT
EACH HEART BEAT.

A-Heart Failure with Reduced Ejection Fraction (HFrEF)



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.

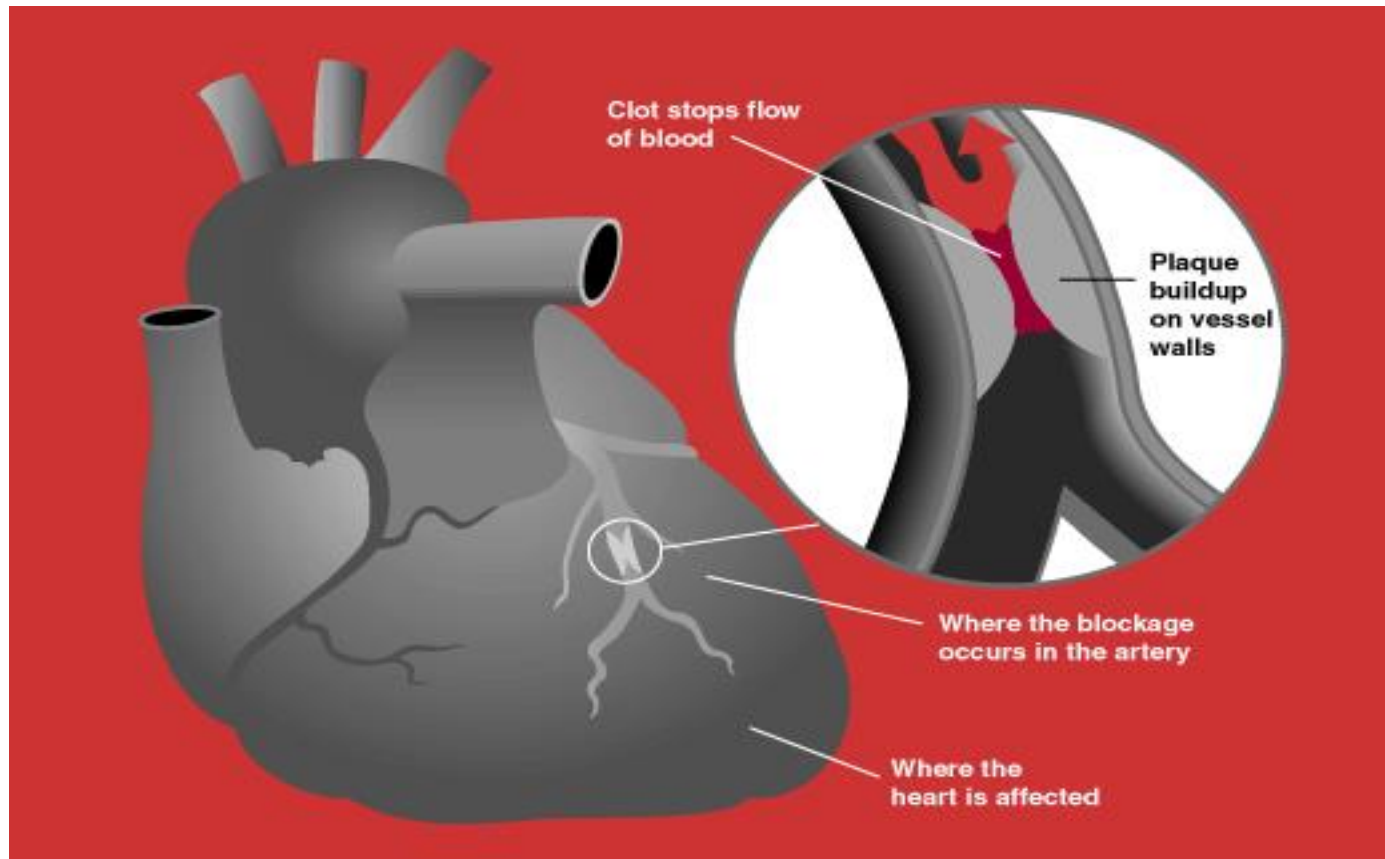
2- **β -Blockers** should be used for hypertension treatment in patients with SIHD. An ACE inhibitor or ARB has been shown to reduce CV events as an **add-on** to a β -blocker.

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.**



D-Diabetes Mellitus

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.**



E-Chronic Kidney Disease

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, andtrandolapril)

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-**D**ihydropyridine 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 $<30 \text{ mL/min/1.73 m}^2$** , 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 **β 1-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 β_2 -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- α 1-Receptor Blockers

1-Prazosin, terazosin, and doxazosin are selective α 1-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 α 1-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 α 2-Agonists

1-Clonidine, guanfacine, and methyldopa lower BP primarily by stimulating α 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 α_1 -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 funduscopy 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.



TQ





2021-2022

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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 (**NSTE**) or ST-segment elevation (**STE**) **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.

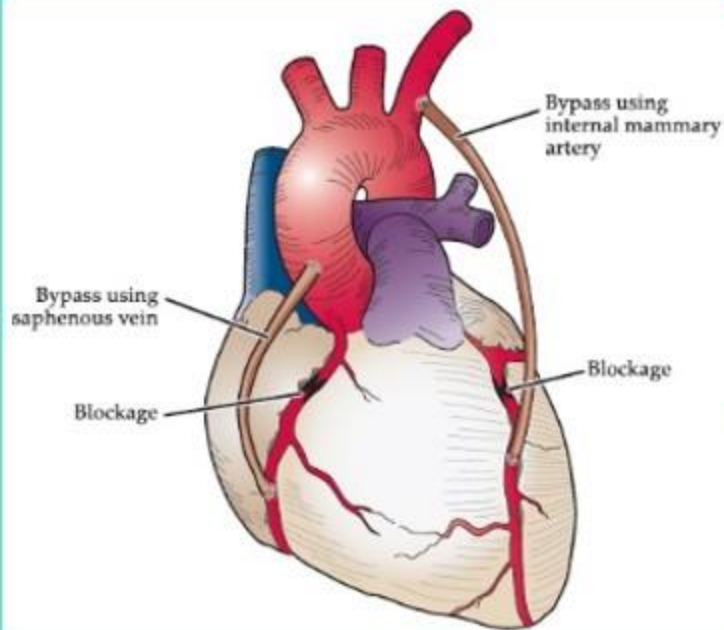


Treatment

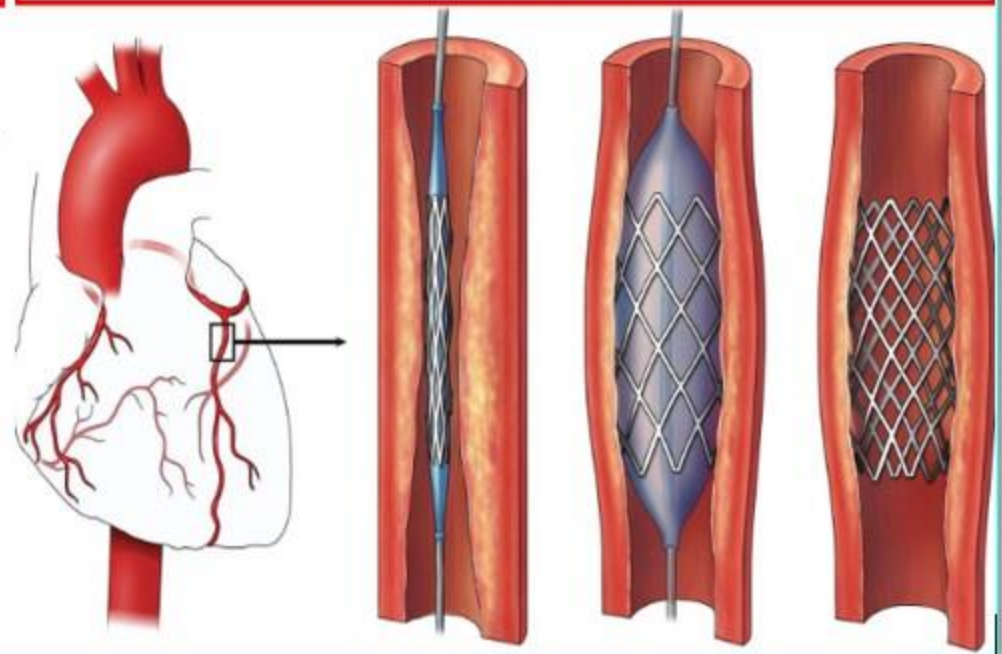
Nonpharmacologic Therapy

Revascularisation

CABG (BYPASS SURGERY)



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 $\geq 130/80$ mm Hg, institute drug therapy in addition to or after a trial of lifestyle modifications.
- ▶ **Diabetes mellitus:** Pharmacotherapy to achieve a target A1C of $\leq 7\%$ 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.

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- ▶ 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 (eg, 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 (eg, hypotension, syncope, renal dysfunction).
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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- **β 1-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 **α 1- 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** (I_{Na}), 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

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition. 2021.



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Anemia

Introduction

- ▶ 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.
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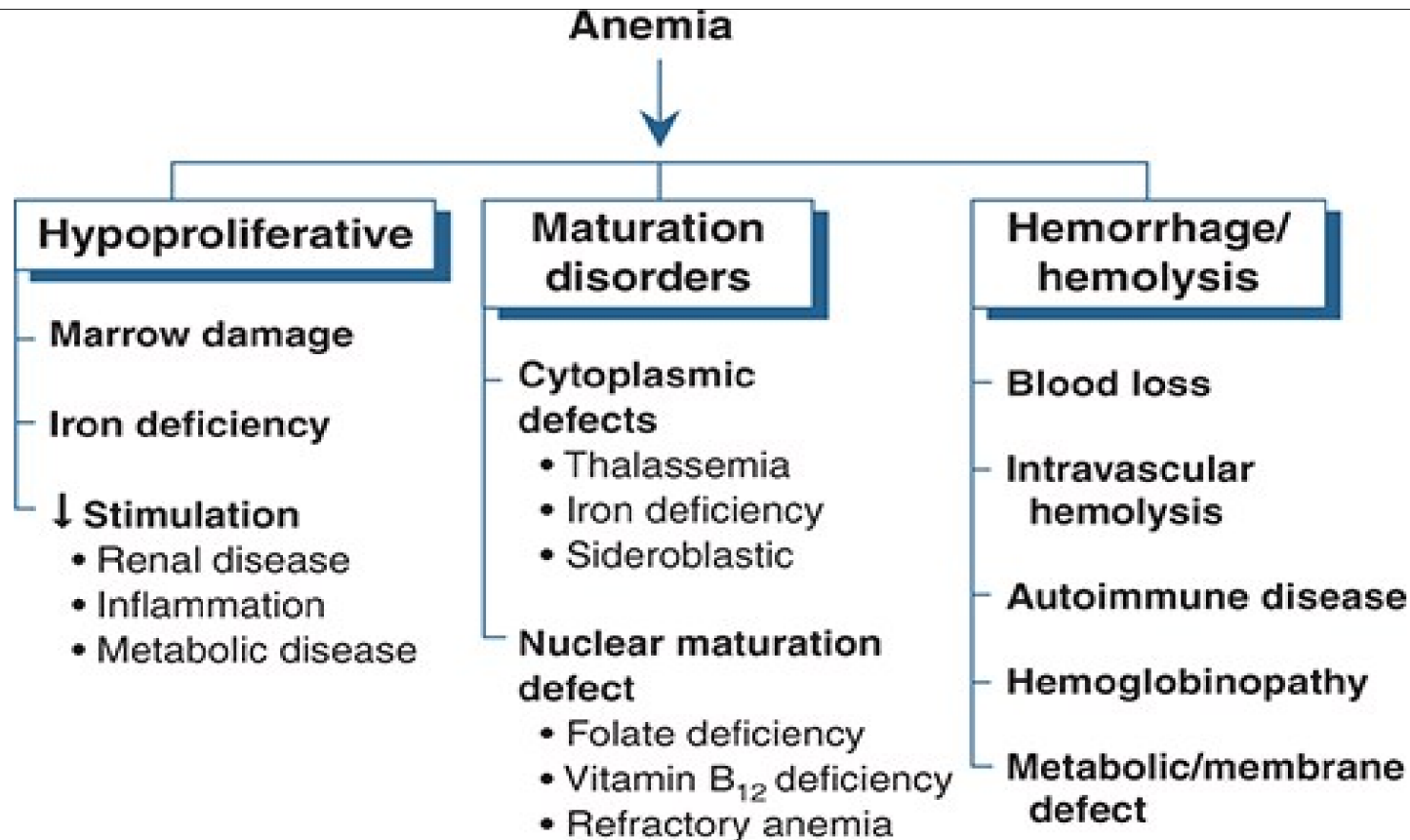
Classification

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.



Functional classification of anemia

- 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 (eg, 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.
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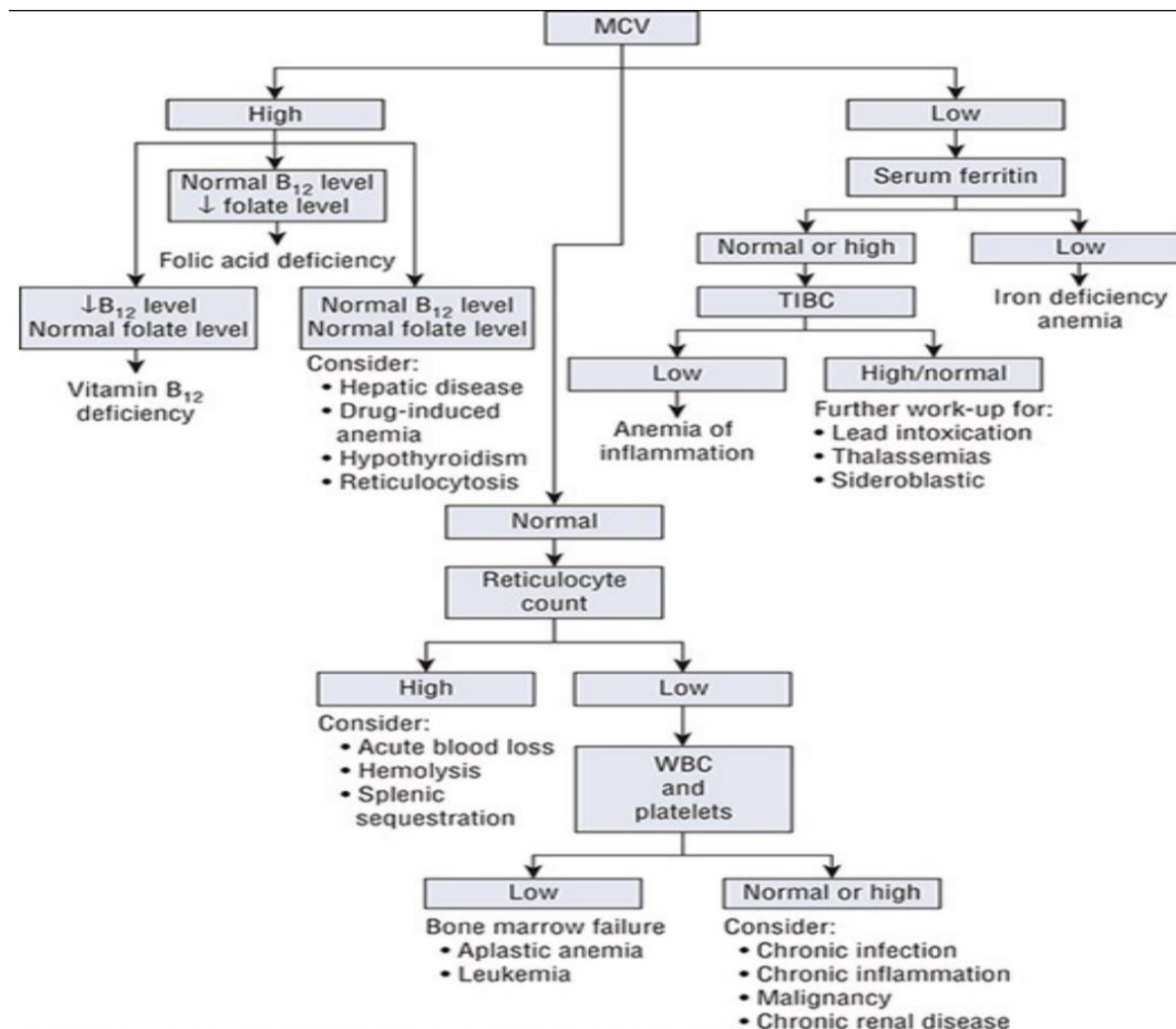
Diagnosis

- ▶ **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



(↓ decreased; 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:

Dose of iron (mg) = whole blood hemoglobin deficit (g/dL) × body weight (lb) or

Dose of iron (mg) = whole blood hemoglobin deficit (g/L) × body weight (kg) × 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.

Iron Salt	Percent Elemental Iron	Common Formulations and Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 60 mg/5 mL syrup 44 mg/5 mL elixir 15 mg/1 mL drops
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28–29 mg/240–246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324–325 mg tablet

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.
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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.



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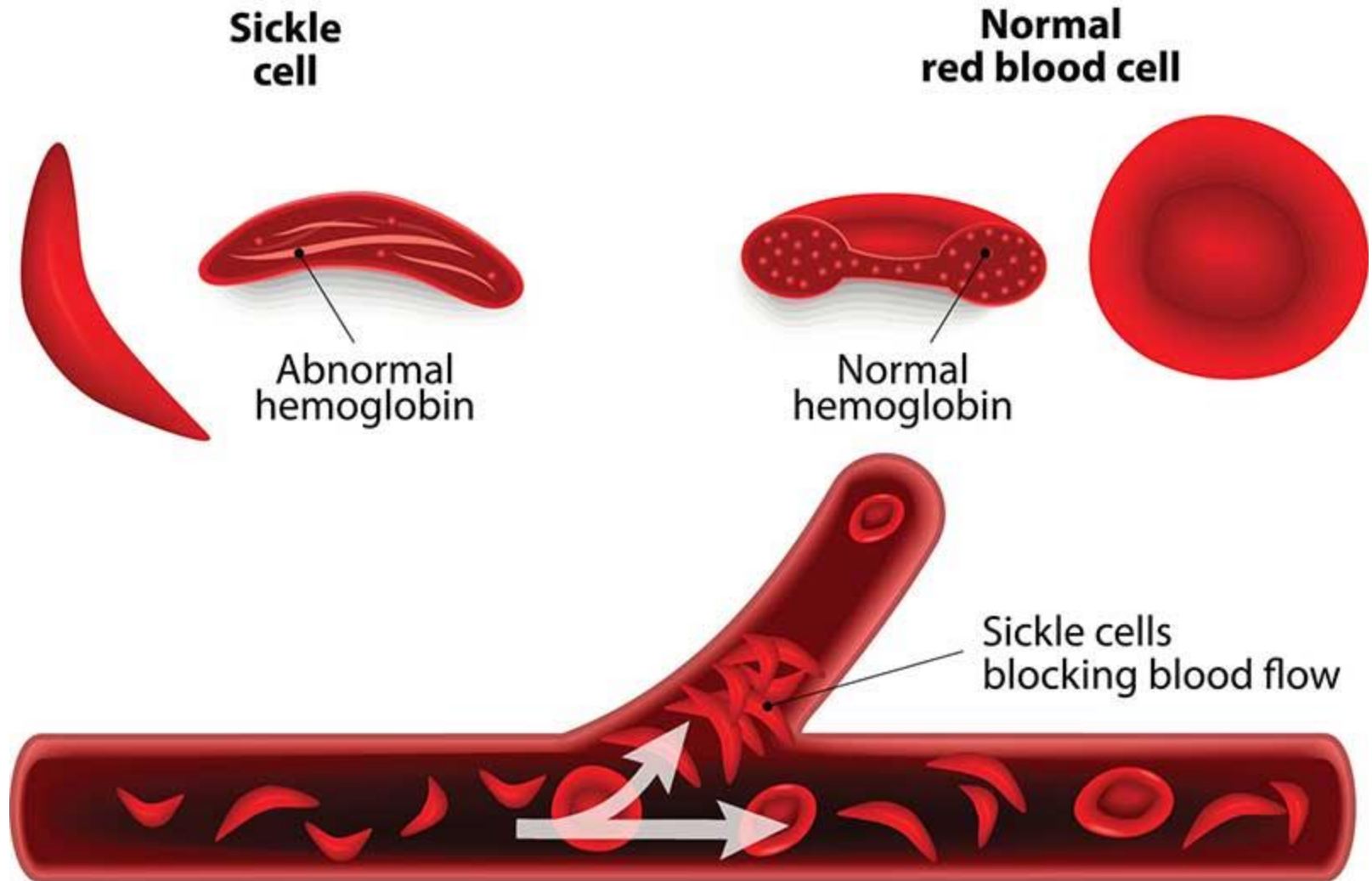
Sickle Cell Disease

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 HbS β 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 (HbS β + -thal and HbS β 0 -thal), and some other rare phenotypes.
-



Introduction



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 (**Table1**).
- ▶ 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

Type	Clinical Features
Sickle cell trait (SCT)	Rare painless hematuria; heavy exercise under extreme conditions can provoke gross hematuria and complications (normal Hb)
Sickle cell anemia (SCA-HbSS)	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])
Sickle cell hemoglobin C (HbSC)	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])
Sickle cell β^+ -thalassemia (HbS β^+ -thal)	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
Sickle cell β^0 -thalassemia (HbS β^0 -thal)	No HbA production; severity similar to SCA; Hb 7–9 g/dL (70–90 g/L; 4.34–5.59 mmol/L) with microcytosis

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.
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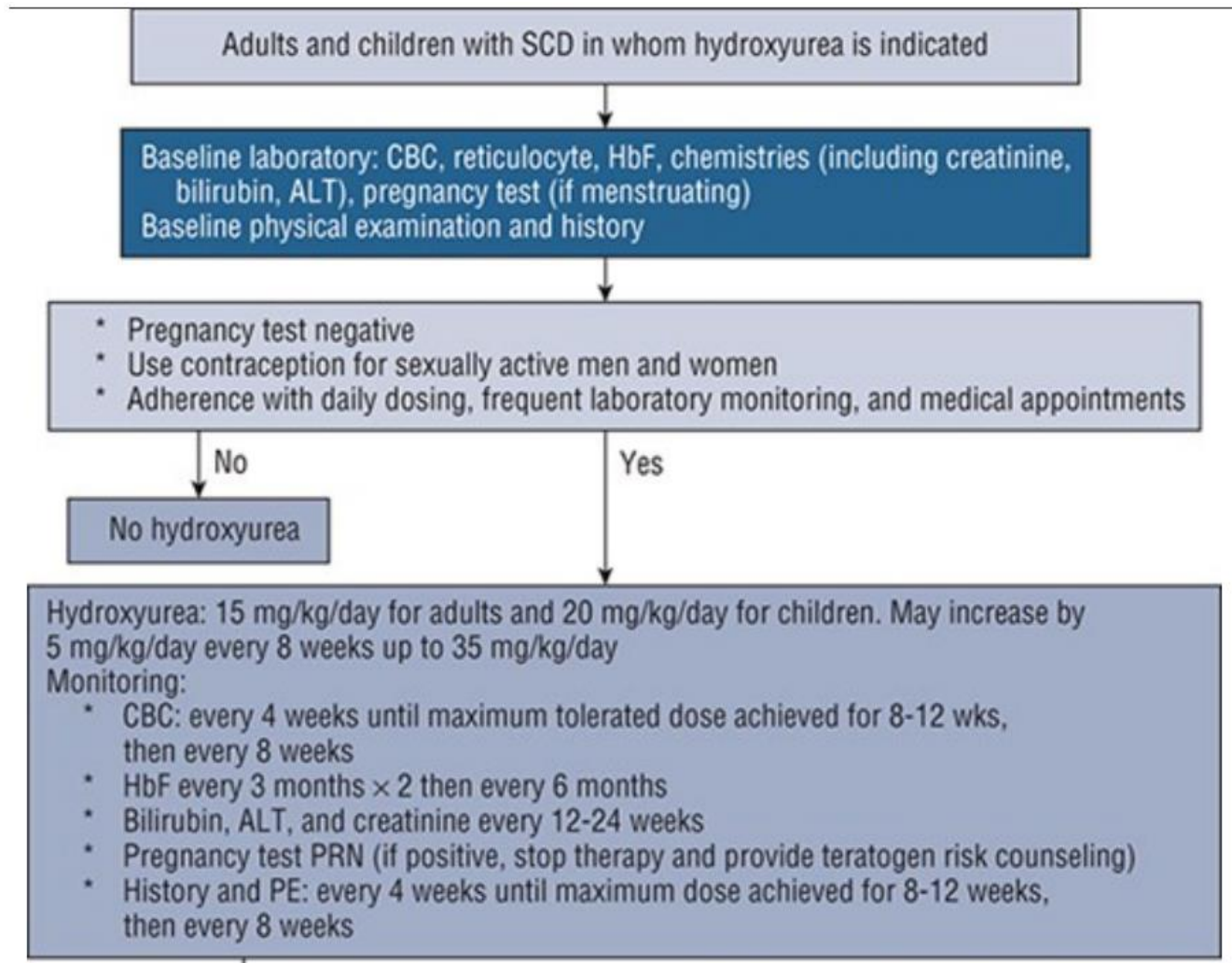


Disease-Modifying Therapies

- ▶ **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**.

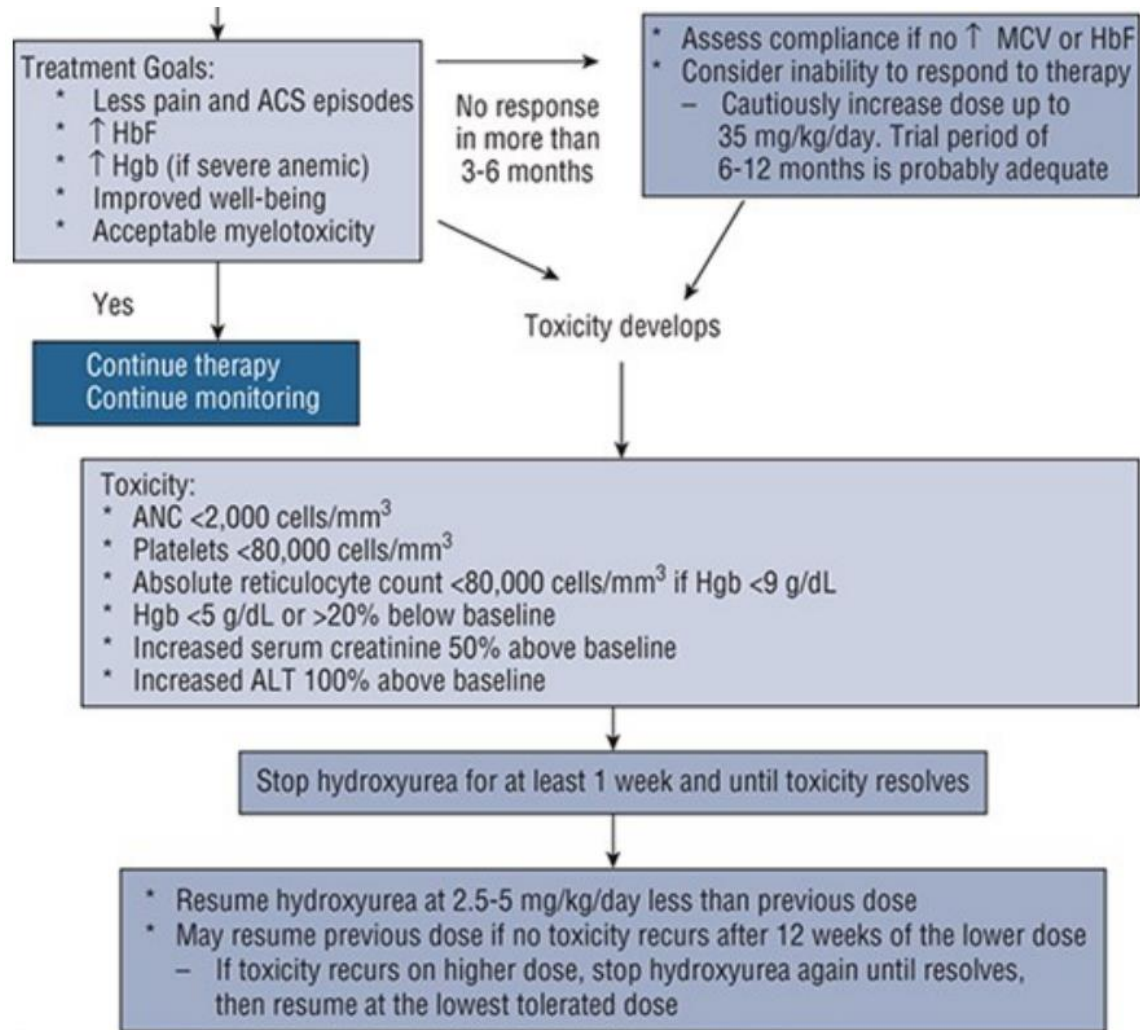


Hydroxyurea



(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



(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.)

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. (eg, 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.



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Heart Failure

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.**

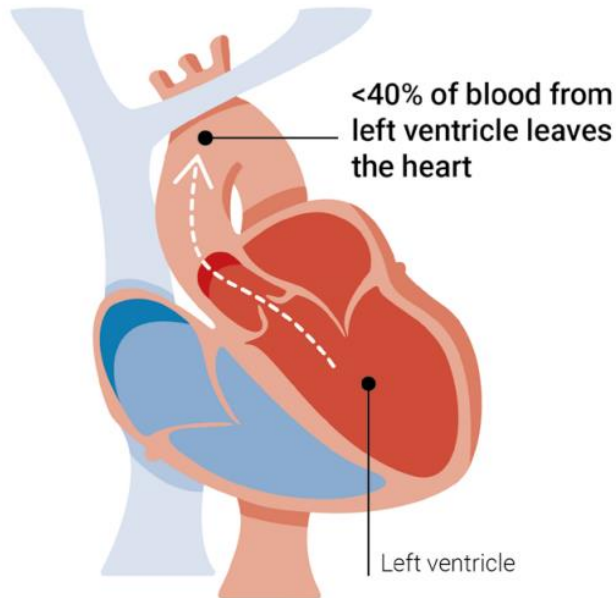
3-HF with reduced systolic function (ie, reduced left ventricular ejection fraction, LVEF) is referred to as **HF with reduced ejection fraction (HFrEF).**

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



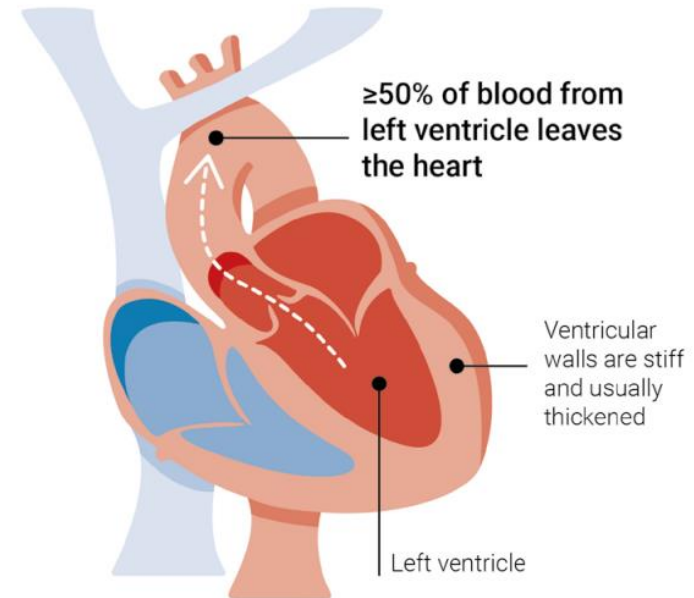
Introduction

HFrEF



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

HFpEF



In HF with preserved ejection fraction (HFpEF), 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**.

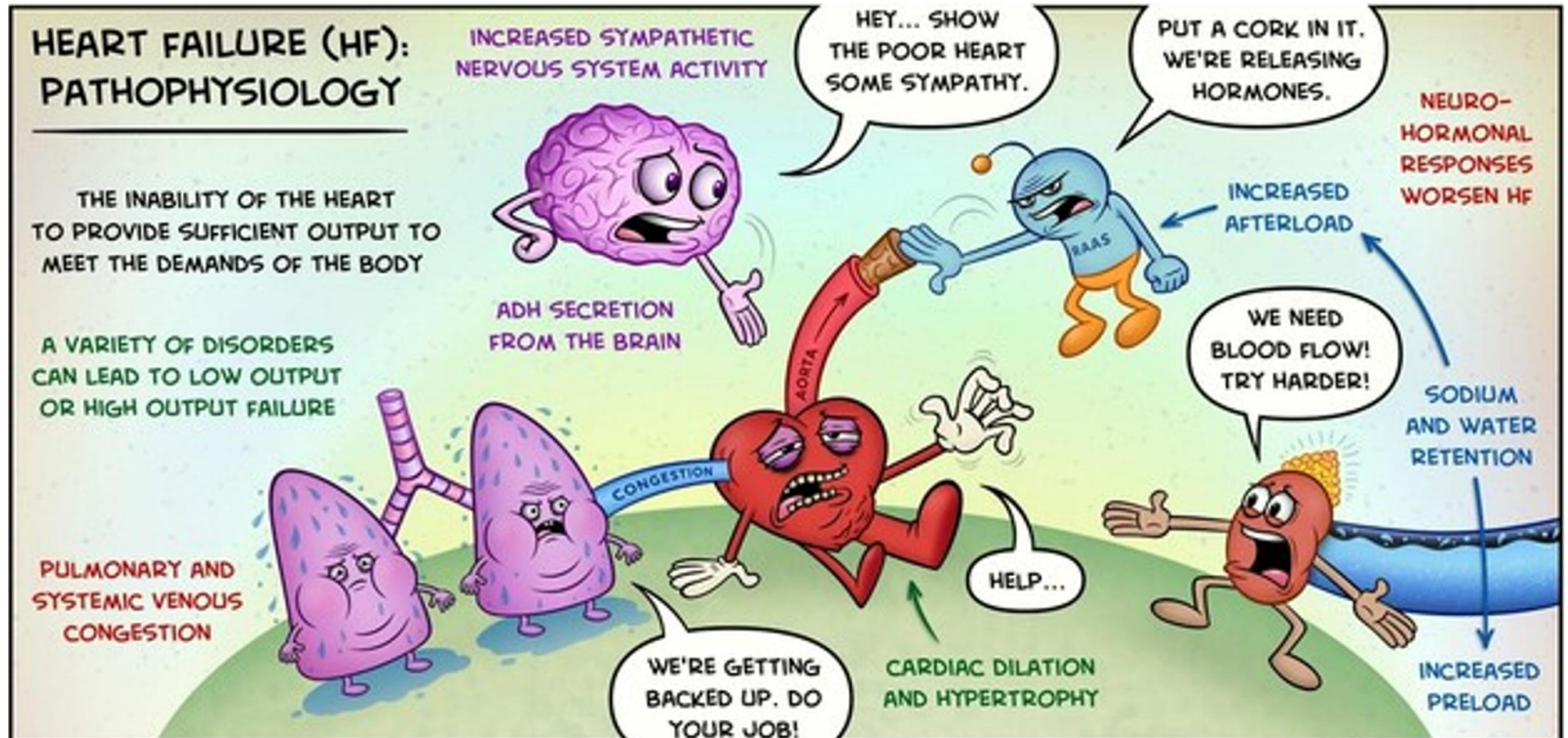
8-The alterations in ventricular function result in **further deterioration in cardiac systolic and diastolic functions** that further promotes the remodeling process.

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



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.



Treatment of chronic heart failure

- ▶ 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.



Treatment of chronic heart failure

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

B-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**.

SACUBITRIL/VALSARTAN MECHANISM OF ACTION



Natriuretic peptides are responsible for salt and water balance in the body



Neprilysin

Neprilysin is an enzyme that breaks down natriuretic peptides, preventing them from doing their job

Angiotensin II is a hormone that causes vasoconstriction and increases aldosterone secretion leading to high blood pressures



- Sacubitril inhibits neprilysin enzymes
- Valsartan blocks angiotensin II receptors

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-Spironolactone also interacts with **androgen and progesterone** receptors, which may lead to **gynecomastia, impotence, and menstrual irregularities** in some patients.



Treatment of chronic heart failure

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 $\leq 35\%$** 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.



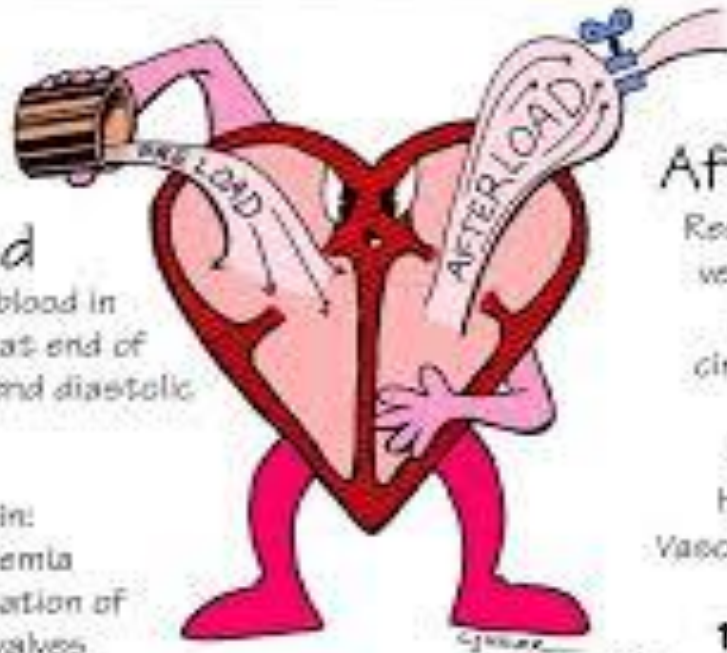
Treatment of chronic heart failure

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

↑ Afterload =
↑ Cardiac workload

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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**.



TQ

