Lecturio Medical Knowledge Essentials – Hypertension

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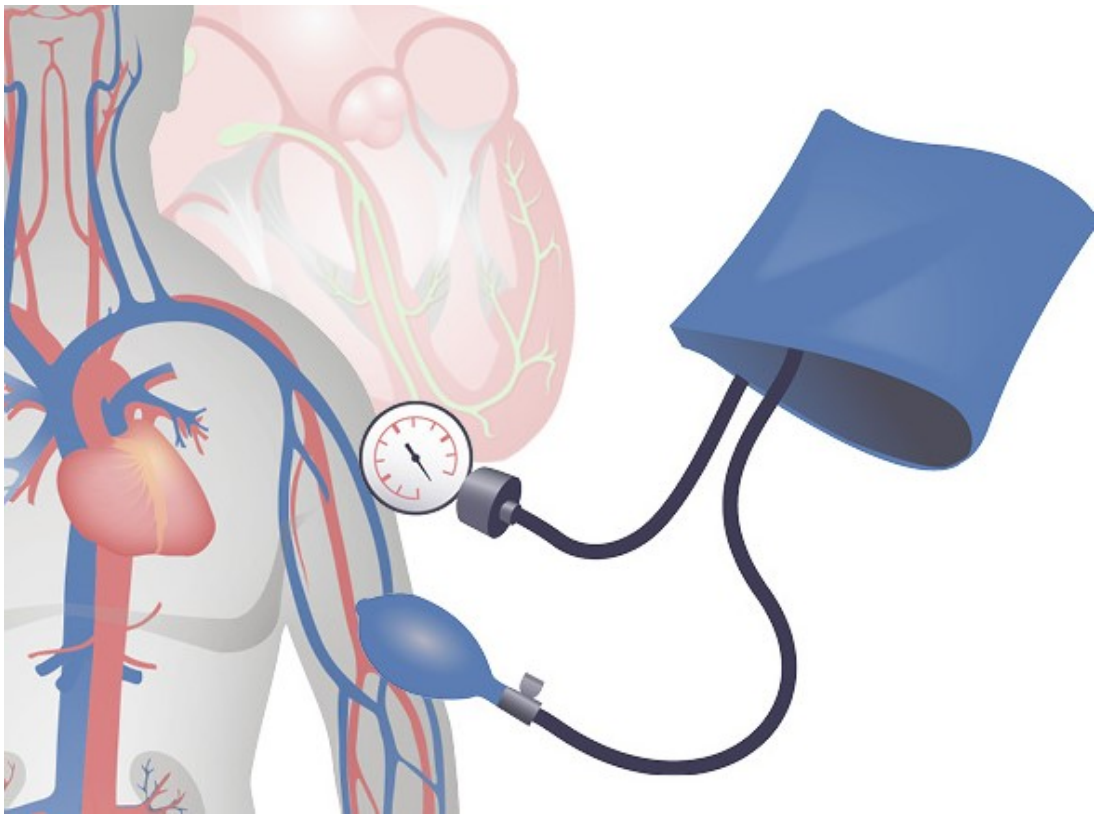

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Hypertension (HTN) is one of the most common chronic medical conditions in the world, affecting one-third to one-half of the population, depending on the definition used for HTN. The current definition of HTN in the USA is a systolic blood pressure (SBP) of ≥130 mm Hg and/or a diastolic blood pressure (DBP) of ≥80 mm Hg, [1][2] but most countries continue to use ≥140/90 mm Hg as the definition for reasons discussed later.[3] The prevalence of HTN increases with age and sex (men > women). Most people with HTN do not have adequate blood pressure control, even in high-income countries,[4] but this is particularly evident in low and middle-income countries, where BP control is often very low, and many hypertensives remain undiagnosed. Hypertension is a major risk factor for multiple diseases, including strokes, heart failure, ischemic heart disease, and acute and chronic kidney disease. It is considered to be a major public health failure that many millions of people in the world with hypertension are not receiving the treatment that they need, since the condition is easy to diagnose and can be treated with low-cost

drugs. Three large studies in lower income countries have shown a dramatic decrease in cardiovascular disease by providing a combination pill (a “polypill,” including atorvastatin, hydrochlorothiazide, either enalapril or valsartan, and with or without aspirin) to those over 50 years of age (in the PolyIran study), regardless of cardiovascular risk factors.[5-7] In the United States, hypertension management is one of the most common reasons for medical office visits.[8].

TIP FOR THE USMLE: This is a **high-yield topic** because it has the four key elements of a high-yield disease or condition: it is **common, serious, diagnosable, and treatable.**

For further review of this topic, including links to lectures by specialists in the field, follow this link: https://www.lecturio.com/concepts/hypertension/

Definitions and Staging Classification

- A diagnosis of HTN requires integration of the measurements made in the clinic with home or ambulatory blood pressure monitoring (ABPM).[1]
- From the 2017 American College of Cardiology/American Heart Association (ACC/AHA), the definitions and staging of hypertension are:
    - Normal systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg
    - Elevated BP: SBP 120–129 mm Hg and DBP <80 mm Hg
    - Hypertension, Stage 1: SBP 130–139 mm Hg or DBP 80–89 mm Hg
    - Hypertension, Stage 2: SBP ≥140 mm Hg or DBP ≥90 mm Hg
    - Treated hypertension: Patients on medication for hypertension, regardless of the BP
    - **Note**: The ACC/AHA stage is established by the higher value, if the SBP and DBP differ in stage.
- The ACC/AHA guidelines have been contested because some medical experts and other professional societies believe that the data is not definitive, that the risk of harm may outweigh the benefit in individual cases, and that the new guidelines are not practical to follow in low and middle-income countries since so many people with HTN in those countries already do not receive treatment at the higher thresholds.[9-11] A systematic review by the Cochrane Organization also noted: “For the general population of persons with elevated blood pressure, the benefits of trying to achieve a lower blood pressure target rather than a standard target (≤ 140/90 mm Hg) do not outweigh the harms associated with that intervention. Further research is needed to see if some groups of patients would benefit or be harmed by lower targets. The results of this review are primarily applicable to older people with moderate to high cardiovascular risk. They may not be applicable to other populations.”[3] HTN is defined by the European Society of Cardiology and European Society of Hypertension (ESC/ESH), the International Society of Hypertension (ISH), and the National Institute for Health and Care Excellence (NICE guidelines), as: “Hypertension, using office-based blood pressure, is defined as: Systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.”[12]

Epidemiology

A person who has an actual measured high blood pressure and/or is taking antihypertensive medication is considered to have HTN.[1] In 2019, a global study using ≥140/90 mm Hg as the definition of HTN found that the prevalence of HTN in adults aged 30–79 years was 32% in women and 34% in men, which was similar to the 1990 levels. These percentages would have increased to an average of approximately 45% if the 2017 ACC/AHA lower cutoff level of ≥130/80 had been used, signifying a global burden of hypertension of at least 1.8 billion people.[2] The prevalence of HTN increases with age (70% of adults ≥65 years have hypertension[13] and body weight. In the United States, the prevalence is higher in Blacks than in Whites or Hispanics, and also higher in rural than in urban environments. Most people with HTN do not have adequate blood pressure control, even in high-income countries, but this is particularly pronounced in low and middle-income countries, where BP control is often very low, and many hypertensives remain undiagnosed. In high-income countries, only 37% of men and 43% of women have their HTN under control, while these percentages drop to 9% for men and 13% for women in sub-Saharan Africa and Oceania.

Etiology

Systemic arterial hypertension (HTN) is divided into two types: primary hypertension (also known as “essential hypertension” because at one time it was believed the high pressure was necessary to keep the vital organs perfused); and secondary hypertension.[14-16]

Primary Hypertension (PH)

This is hypertension of unknown cause. Depending on the diagnostic method used, approximately 80–95% of hypertensive patients have PH, which is really the final manifestation of different underlying pathophysiologies. 60–70% of PH in adults has been attributed to being overweight or obese. Peripheral vascular resistance (PVR) is increased, and cardiac output is normal or decreased in most patients with long-standing PH; however, in younger patients, the PVR may be normal, with increased cardiac output. Plasma renin activity (PRA) is increased in approximately 10–15% of individuals with PH (called “vasoconstrictor type” of HTN), while PRA is decreased in ~ 25% (called “volume-dependent” or “low-renin hypertension;” which is more common in African Americans). These underlying mechanisms help explain why not all PH patients have the same response to the same medication: a person with high-renin HTN would likely respond to a vasodilator, and a low-renin HTN patient would likely respond to an aldosterone antagonist like spironolactone since aldosterone tends to be elevated in low-renin conditions.

The risk factors associated with primary hypertension are:[17]

- Obesity and general weight gain (accounts for 60–70% of PH; central adiposity is associated with higher risk)
- Age: advancing age is associated with weight gain, and especially associated with ↑SBP
- Family history: Genetic factors can affect blood pressure increases by 30–50% [16]
- Race: HTN tends to be more common and more severe in people with African ancestry
- High-sodium diet: >3 g/day of sodium chloride consumption increases the risk

- Excessive alcohol consumption
- Lack of exercise
- Reduced adult nephron mass, from any cause—genetic/congenital, drugs, malnutrition, infections

Secondary Hypertension

- This category comprises 5% to 10% of patients with HTN, and indicates an underlying and potentially reversible cause.[15] Many causes may coexist with primary hypertension and make adequate blood pressure control difficult to achieve. [1]
- Suspect if:
    - Unusual presentation of HTN (onset at < 30 or > 55 years; abrupt onset of HTN in a patient with previously normal BP; or elevation in blood pressure in a well-controlled hypertensive)
    - Drug-resistant hypertension
    - Clinical clues, e.g., such as an abdominal bruit → may indicate possible renovascular hypertension; low serum potassium → possible primary aldosteronism
- **The Four Major Causes of Secondary Hypertension:**
    - **Primary aldosteronism (PA)** – Triad of hypertension, hypokalemia (only in 50%), metabolic alkalosis. Elevated ratio of plasma aldosterone to plasma renin activity; chronic licorice intake can mimic PA.
    - **Renovascular hypertension** – often due to fibromuscular dysplasia in younger patients and to atherosclerosis in older patients; may have abdominal bruit
    - **Primary kidney disease** – Acute or chronic kidney disease
    - **Obstructive sleep apnea (OSA)**: typical patient is obese man who snores loudly; > 50% of people with OSA have HTN
- **Less Common Cause of Secondary Hypertension:**
    - **Medications,** both prescription and over-the-counter: nonsteroidal antiinflammatory agents, especially if used chronically; oral contraceptives; antidepressants; corticosteroids;decongestants; various weight-loss medications; sodium-containing antacids, if used chronically; stimulants, including amphetamines and methylphenidate; erythropoietin; cyclosporine or tacrolimus; atypical antipsychotics; angiogenesis inhibitors; tyrosine kinase inhibitors; and illegal drug use, especially methamphetamines and cocaine
    - **Endocrine disorders:** hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing syndrome
    - **Pheochromocytoma:** 50% have paroxysmal hypertension; others appear to be primary hypertension; rare cause
    - **Coarctation of the aorta:** Major cause in young children, but also diagnosed in adults

The mechanism of renovascular hypertension is mainly due to renal ischemia. Renal artery stenosis results in an increased level of renin and angiotensin I and II. These are associated with increased vasoconstriction, hence, hypertension and an increased sympathetic tone. Aldosterone production is also increased in these patients which results in increased retention of sodium. The increased retention of sodium is associated

with increased water retention and can lead to extracellular blood volume. The interplay between these 2 mechanisms is the main cause of hypertension in this group of patients.

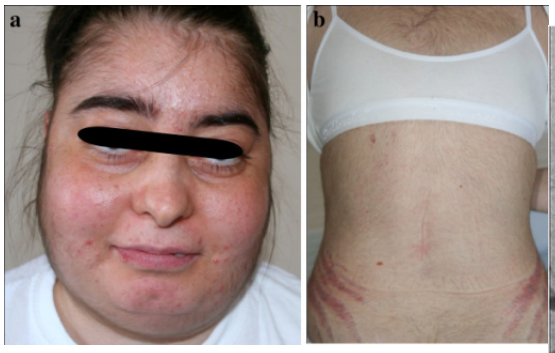


Image: Patient with Cushing syndrome due to hypercortisolism showing buffalo hump, moon face, and classical purple abdominal striae. "Cushing-Syndrom" by Celik O, Niyazoglu M, Soylu H, Kadioglu P. License: CC BY 2.0

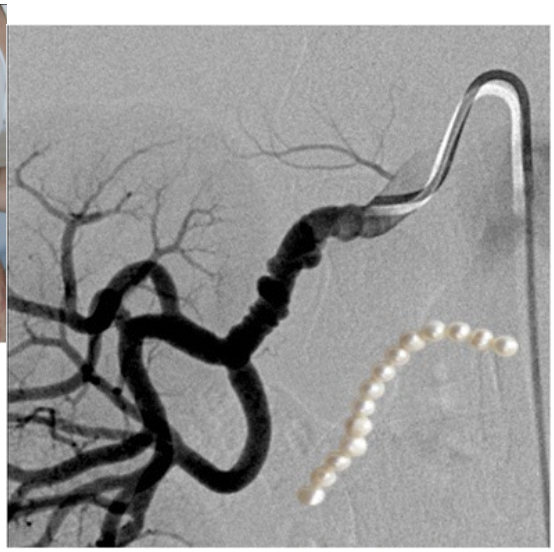


Image: Digital subtraction angiogram in a 35-year-old woman with uncontrolled hypertension demonstrates contiguous relative stenoses alternating with fusiform aneurysmal dilatation of the right renal artery due to fibromuscular dysplasia resembling a string of beads (inset). Fibromuscular dysplasia is characterized by fibrous or muscular hyperplasia in one or more layers of the renal artery wall, producing this appearance. By: Bryan Buckley, et al. License: CC BY 4.0

Another type of arterial hypertension is **hypertensive disease of pregnancy**. Risk factors include increasing maternal age and multifetal pregnancies.

Hypertensive disorders of pregnancy are divided into:

- Gestational hypertension (hypertension not associated with proteinuria)
- Preeclampsia (hypertension associated with proteinuria); it is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation, and presents up to 4-6 weeks postpartum.
- Eclampsia (new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia

Pathophysiology

Blood is delivered to the tissues and flow occurs because of the pressure difference established by the pumping action of the heart. This relation between the pressure difference and the flow can be described by the important equation: MAP = CO x PVR, where MAP = mean arterial pressure (= diastolic pressure + ⅓ [systolic pressure – diastolic pressure]), CO = cardiac output (= stroke volume x heart rate), and PVR = total peripheral resistance. At its basic level, this equation emphasizes that an elevation of mean blood pressure can only occur if there is an increase in cardiac output (CO), an increase in total peripheral vascular resistance (PVR), or a combination of both. The main factors which determine blood pressure are the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the plasma volume, which is mostly regulated by the kidneys. Increased peripheral vascular resistance (PVR) is the hallmark of established hypertension, but altered cardiac function also probably contributes to the raised blood pressure.[18] An increase in calcium intake slightly reduces both systolic and diastolic blood pressure in normotensive people, indicating a possible role in the prevention of hypertension.[19] The underlying pathogenesis of primary hypertension is not well-understood, but many genetic and environmental factors are involved.

Clinical Features

Most people with hypertension have no signs or symptoms, even with severe HTN; that is why it is often called “the silent killer.” Some people with severe HTN may have non-specific signs and symptoms, including headaches, shortness of breath, nosebleeds, fatigue, confusion, vision alterations, chest pain, palpitations, or hematuria.

Subtypes and Variants

Special forms of arterial hypertension are isolated office hypertension and isolated ambulatory hypertension.[1]

1. White-coat hypertension (“White-coat effect”)

- Defined as a BP which is consistently elevated by office readings only when in the physician’s office, while measurements taken at home and during ambulatory blood pressure monitoring are normal.
- Not true hypertension

2. Isolated systolic hypertension:

- Defined as an increase in systolic blood pressure with diastolic blood pressure within normal limits
- Occurs commonly in the elderly due to decreased arterial elasticity/increased stiffness of the arteries
- Having a high systolic blood pressure for a long period of time can increase the risk of strokes, heart disease and chronic kidney disease.

3. Masked hypertension: This is BP that is consistently elevated by out-of-office measurements but normal at the office.

Diagnostics

Medical History and Physical Examination

Gathering a patient's medical history is essential because it helps to discover risk factors, previous blood pressure measurements, and symptoms referable to hypertensive-related target organ damage, including ischemic heart disease, cerebrovascular disease, and chronic kidney disease. It is very important to ask patients about their current medications, previous illnesses, and family history.

The patient's physical examination should include checking the radial and the femoral pulses and performing abdominal auscultation which may help identify a bruit associated with renal artery stenosis, although this is not a sensitive test for RAS.

Furthermore, it is essential to look for signs of heart failure and left ventricular hypertrophy. The fundi of the eyes should be examined as well to evaluate for possible hypertensive retinopathy, which will show progressively severe changes ranging from mild arteriolar narrowing → focal arteriovenous nicking → retinal hemorrhages and exudates → papilledema (grade IV hypertensive retinopathy).

Measuring Blood Pressure

Except for diagnostic severe hypertension (SBP ≥180 mm Hg and/or DBP ≥120 mm) or asymptomatic Stage 2 hypertension, all patients who have an elevated office blood pressure should have out-of-office blood pressure measurements for confirmation of the presence of true HTN. Automated and validated oscillometric BP monitors are preferred to stethoscope-based manual methods, both in the office and at home. For home measurements, the patient measures their BP once in the morning and once in the evening for 7 days. The first day of readings and the remaining 12 measurements are averaged. Hypertension is diagnosed if the mean home BP is ≥130 mm Hg systolic or ≥80 mm Hg diastolic. 24-hour ambulatory blood pressure monitoring (ABPM) is an alternative if adequate home blood pressures cannot be obtained or if there is doubt about the validity of home readings.

All individuals 18 years or older should be screened for HTN, with annual evaluation for those > 40 years old or those with risk factors for HTN. Younger adults with no risk factors should be evaluated every 3–5 years.

Laboratory Diagnostics

All patients with a new diagnosis of hypertension should have the following tests:

- Electrolytes (including calcium) and serum creatinine (to calculate the estimated glomerular filtration rate and determine the presence of kidney disease)
- Fasting glucose (to check for diabetes)
- Urinalysis (moderately increased albuminuria [previously called "microalbuminuria"] which is associated with an increased incidence of cardiovascular disease)
- Complete blood count
- Thyroid-stimulating hormone
- Lipid profile
- Electrocardiogram

- Calculation of 10-year atherosclerotic cardiovascular disease (ASCVD) risk: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/: in patients with stage 1 hypertension, ASCVD risk assessment can guide the need for treatment.

Extensive evaluation for secondary causes of HTN is not justifiable for all patients with primary hypertension, but rather only a targeted approach is recommended if there is an atypical presentation or there is a clinical clue that a secondary cause may be present.

Treatment

Non-pharmacological treatment (lifestyle modifications): alone or with antihypertensive drug therapy:

- Dietary salt restriction: can reduce SBP/DBP by 4.8/2.5 mm Hg
- Potassium supplementation (best by dietary modification): unless chronic kidney disease or using medications that reduce potassium excretion
- Weight loss: can reduce BP 0.5 to 2 mm Hg for every 1 kg lost
- Dietary Approaches to Stop Hypertension (DASH) diet: high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts and low in sweets, sugar-sweetened beverages, and red meat: can reduce SBP/DBP by 6/4 mm Hg
- Exercise: Aerobic, dynamic resistance, and isometric resistance exercise at least 3–4 x per week of moderate-intensity aerobic exercise lasting approximately 40 minutes; can reduce SBP/BP by 5/3 mm Hg
- Limited alcohol intake: Adult men and women with hypertension should consume no more than two and one drinks/day respectively

Pharmacological Treatment

Blood pressure targets are based upon the patient’s risk for having a future cardiovascular event. In general, more aggressive blood pressure goals are indicated for higher-risk patients. It is recommended to start pharmacological therapy as a monotherapy. In the event that blood pressure values are 20/10 mm Hg above goal or in cases of comorbidities, primary combination therapy should be considered.[20]

First-line medications include:

- Thiazide diuretics
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Calcium channel blockers

While the above medications are considered as primary antihypertensives, they can still be combined.

Secondary antihypertensives are used when primary medications do not work or when there are special indications such as in hypertensive patients who also have ischemic heart disease.

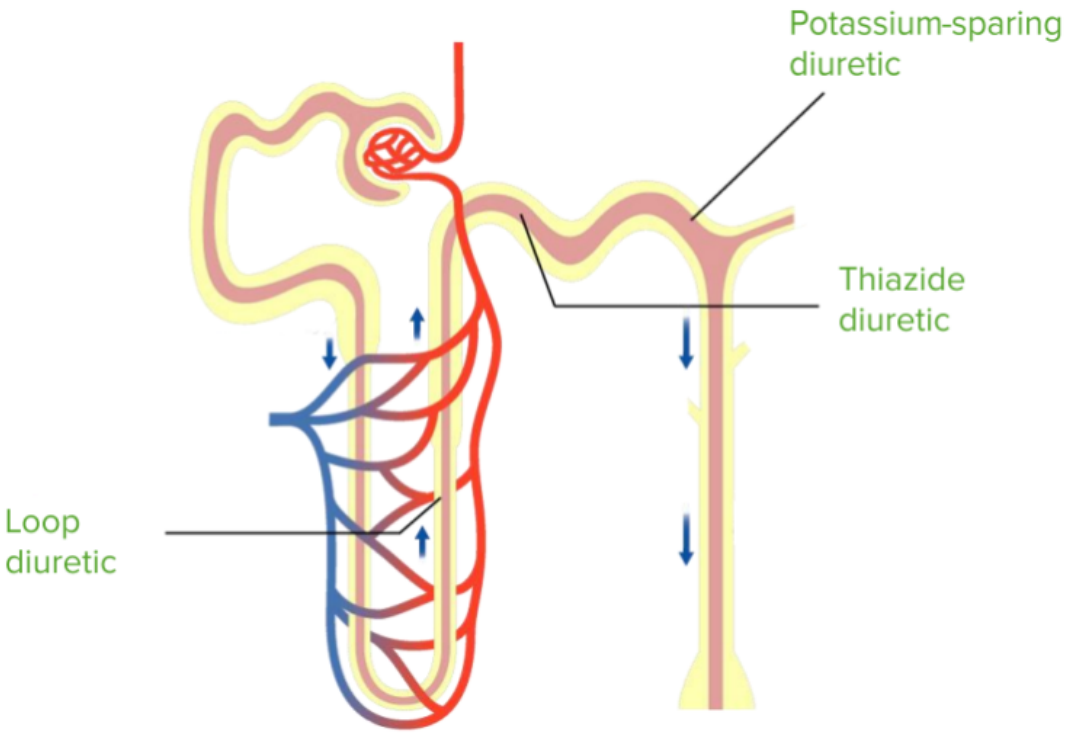
Secondary antihypertensives include:

- Loop diuretics
- Potassium-sparing diuretics
- Beta-blockers

- Direct renin inhibitors
- Alpha-1 blockers
- Central alpha-2 blockers
- Direct vasodilators

Diuretics

Primary sites of action [20,21]



Sites of action of common diuretics used in the treatment of hypertension. Image by Lecturio.

Thiazide Diuretics

- Excellent first-line therapy alone or in combination with other agents
- Mechanism: they bind the Cl − site of the Na+/ Cl − co-transport system in the distal convoluted tubule, thereby causing loss of sodium and chloride ions in the urine.
- The effect on blood pressure is limited because the contraction in blood volume stimulates renin secretion, leading to angiotensin formation and aldosterone secretion, which raises blood pressure
- Generic and therefore inexpensive
- Shown to reduce cardiovascular-related events, for example, stroke, in patients with hypertension
- Examples: Chlorothiazide, chlorthalidone, hydrochlorothiazide (HCTZ), indapamide, metolazone

Adverse effects (AEs) of thiazide diuretics:

- Hypokalemia (low blood potassium level) is particularly a problem with chlorthalidone (dose-related, may affect clinical outcome)
- Glucose intolerance ⇒ diabetic tendency
- Gout

- Kidney damage

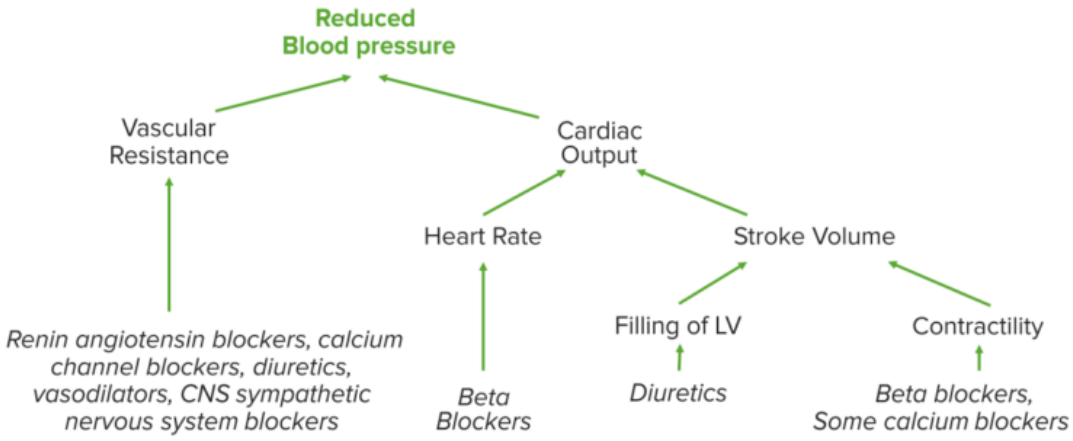
Loop Diuretics

- Mechanism:
    - Act on the thick ascending limb, inhibiting the Na+/ K+/ 2Cl− carrier in the lumenal membrane by combining with its Cl− binding site.
    - Initial vasodilator effect by unknown mechanism (s); intravenous administration of furosemide to patients with pulmonary edema caused by acute heart failure can be useful.
- Loop diuretics are the most powerful diuretics because they can cause the excretion of 15%–25% of the filtered Na+, which is delivered to the distal nephron, causing loss of both H+ and K+.
- The plasma concentration of HCO3− increases because plasma volume is reduced while HCO3− is not excreted, producing a form of metabolic alkalosis known as “contraction alkalosis.”
- Examples: furosemide (most commonly used), bumetanide and torsemide; ethacrynic acid (rarely) if there is allergy to sulfonamides

Adverse effects of loop diuretics:

- Excessive Na+ and water loss—especially in elderly patients—can cause
- hypovolemia and hypotension.
- Hypokalemia and metabolic alkalosis; can be serious.
- Hyperuricemia: can precipitate acute gout
- Hearing loss: usually at high doses, may be worsened by concomitant use of other ototoxic drugs such as aminoglycoside antibiotics
- Hypomagnesemia: not often recognized

Antihypertensive Drugs: Hemodynamic Mechanism of BP Reduction



Mechanisms of action of various anti-hypertensive drugs. Different classes of medications decrease blood pressure by decreasing the influence of one or more of the different factors that contribute to maintain arterial pressure. Cardiac output and peripheral vascular resistance the two determinants of arterial pressure. Cardiac output = stroke volume x heart rate, and stroke volume depends on myocardial contractility and the volume of the vascular compartment. Peripheral resistance is determined by the functional and anatomic changes in small arteries (lumen diameters of 100-400 µm) and arterioles. With reference to the diagram above, for example, angiotensin converting enzyme (ACE) blocks the conversion of angiotensin I to angiotensin II (a powerful vasoconstrictor), so peripheral vascular resistance is decreased. Beta blockers decrease heart rate (and myocardial contractility), thereby decreasing the stroke volume and the cardiac output. Diuretics decrease the vascular volume, at least in the short term, which decreases LV filling (so the stroke volume is decreased), and some (e.g., hydrochlorothiazide) may also act as vasodilators in the long term. Some calcium channel blockers decrease contractility, which decreases stroke volume. Image by Lecturio.

Renin-angiotensin Aldosterone System

The kidney is central to blood pressure control through the juxtaglomerular apparatus. Baroreceptors in the arterial system inform the central nervous system about the level of blood pressure. The signals from baroreceptors lead to changes in autonomic nervous system activity. Renin initiates a biochemical sequence that eventually converts angiotensinogen produced in the liver into angiotensin, a strong vasoconstrictor. Angiotensin stimulates release of aldosterone from the adrenal gland which causes the kidney to retain salt (NaCl) and water. Angiotensin stimulates the release of antidiuretic hormone from the pituitary gland which causes the kidney to retain water.

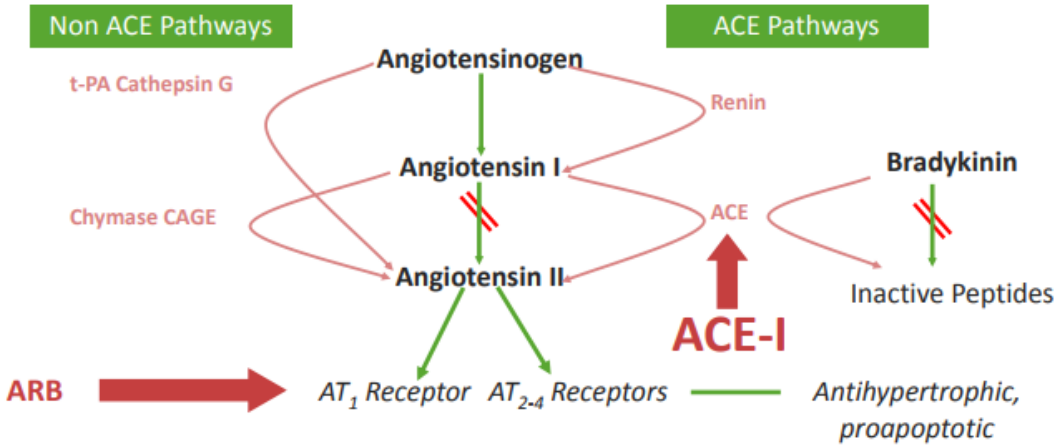


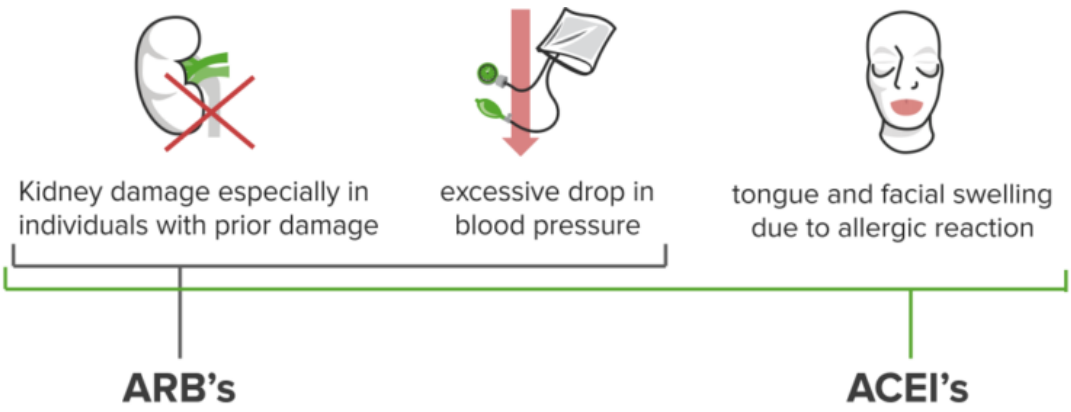
Diagram showing the renin-angiotensin system and related molecules. Many molecules are involved. Angiotensin-converting enzyme inhibitors (ACEIs) inhibit the conversion of angiotensin I to angiotensin II, which can still be produced by enzymes in the non-ACE pathway, such as tissue plasminogen activator (t-PA), cathepsin G, chymase, and chymostatin-sensitive angiotensin II-generating enzyme (CAGE). ACEIs also raise the levels of bradykinin, which provides potent and important cardioprotective benefits, by inhibiting its degradation. One disadvantage of ACEIs is that the presence of non-ACE pathways results in continued low-level production of angiotensin II, despite the inhibition of ACE. Angiotensin II type 1 receptor blockers (ARBs) are selective ligands of AT1 receptors; these drugs can bypass the limitations of ACE escape phenomena and non-ACE sources of angiotensin II formation. Image by Lecturio.

This system is part of the body's defenses against dehydration and/or blood loss. The purpose is to restore blood volume to normal as quickly as possible.

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) include:

- Captopril — ACEi
- Enalapril — ACEi
- Lisinopril — ACEi
- Ramipril — ACEi
- Losartan — ARB
- Candesartan — ARB
- Valsartan — ARB

AE's with ACEis and ARBs — 1st line Rx



Possible adverse effects of ACE inhibitors and ARBs. Image by Lecturio.

Aldosterone Antagonists

- For resistant hypertension despite potent diuretic therapy
- Mechanism of action: They block the effects of aldosterone on the renal distal convoluted tubule and collecting duct, thereby decreasing sodium reabsorption and potassium excretion.

Aldosterone Inhibitors: Spironolactone and Eplerenone

Spironolactone. However, eplerenone is less potent and often requires twice-daily dosing (at 50 to 100 mg) to be as effective for blood pressure lowering. An eplerenone dose of 50 mg once daily can be prescribed as an initial trial, with dose and frequency escalations undertaken as needed to achieve blood pressure control.

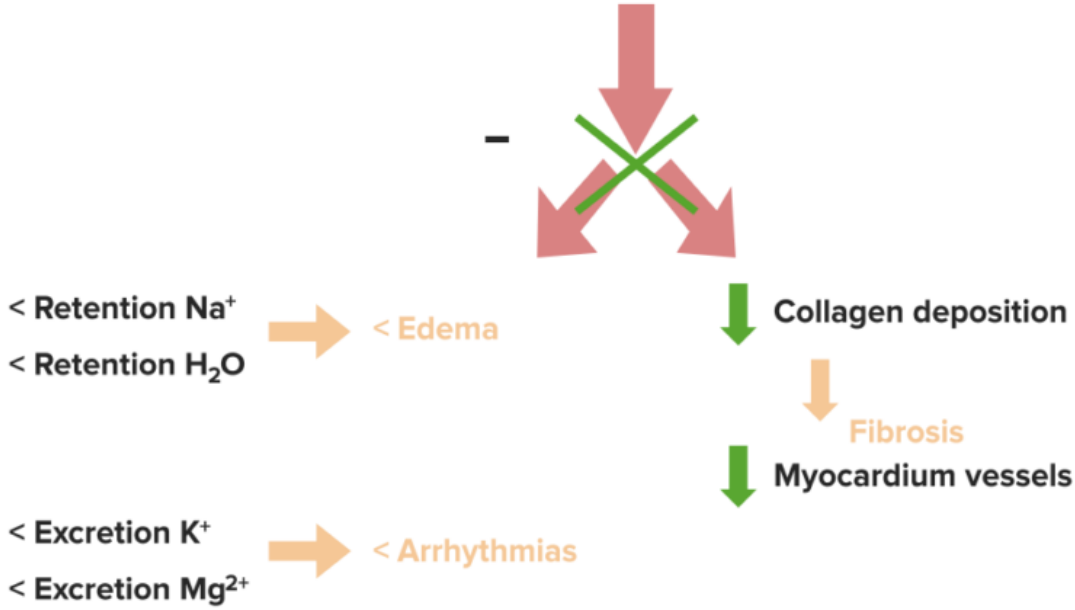


Diagram showing the cardioprotective effects of aldosterone inhibitors. The red arrow at the top represents inhibited aldosterone, and the green "X" at the tip of the arrow represents its inhibition, which leads to (in the left column) decreased retention of sodium and water, and therefore less edema, and decreased excretion of potassium and magnesium, thereby reducing the risk of arrhythmias. The right column shows that there is less collagen (i.e., less fibrosis) and pathologic remodeling of the myocardium and vessels in the presence of an aldosterone inhibitor because aldosterone is a potent inducer of inflammation and oxidative stress which lead to fibrosis (the final manifestation of inflammation). Image by Lecturio.

Adverse effects of aldosterone antagonists

- Hyperkalemia: need to monitor potassium levels!
- Spironolactone → gynecomastia, breast tenderness, and erectile dysfunction (increases with higher doses)
- Eplerenone: more specific and without the side effects of spironolactone but less potent (may need twice-a-day dosing)

Beta-blockers

Beta-blockers reduce cardiac output and decrease renin release by the kidney. They are considered as second-line antihypertensive agents, especially in people > 60 years of age, and include:

- Propranolol
- Metoprolol
- Atenolol
- Carvedilol
- Bisoprolol
- Labetalol

Adverse effects:

- May worsen heart failure and asthma (so begin with very low doses)
- Risk of bradycardia and heart block as the dose is increased
- Impaired glucose tolerance and an increased risk of new onset diabetes
- Fatigue and weakness: may resolve with time or by dose reduction

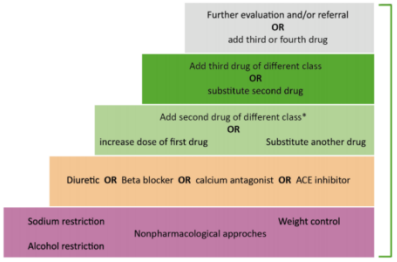
Calcium Channel Blockers (CCBs)

- CCBs are first-line medications in patients with abnormal kidney function.
- They reduce peripheral resistance and blood pressure by dilating arterioles (the resistance vessels).
- The mechanism of action involves inhibition of calcium influx into arterial smooth muscle cells.
- There are two major classes of CCBs:
    - Dihydropyridine CCBs, e.g., amlodipine, nifedipine
        - Adverse effects:
            - Reflex tachycardia due to vasodilation and hypotension, can worsen ischemic symptoms in angina due to an increase in myocardial oxygen demand
            - Can worsen proteinuria in patients with nephropathy
    - Non-dihydropyridine CCBs
        - Verapamil: negative inotropic effect, minimal vasodilation
        - Diltiazem: negative inotropic effect with vasodilation but less than dihydropyridine CCBs

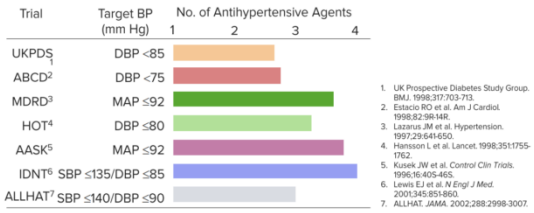
Other Pharmacological Agents Occasionally used

in the treatment of Hypertension

- Minoxidil—very potent blood vessel dilator; also used for hair growth in cases of androgenic alopecia.
- Clonidine—blocks sympathetic activity in the brain and leads to decrease in vascular resistance
- Peripheral sympathetic receptor blockers in vascular smooth muscle —alpha-blockers



Other therapy in hypertension. Image by Lecturio.



Average number of antihypertensive agents used to achieve target blood pressure. Image by Lecturio.

Possible Drug Combinations

Double combination options consist of administering a diuretic in combination with a beta-blocker, a long-acting calcium channel blocker, ACE inhibitors, or ARBs.

An alternative is the combination of a calcium channel blocker with a beta-blocker, ACE inhibitors or ARBs.

Investigators involved in three large randomized controlled studies In lower-income countries concluded that fixed-dose combination treatment strategies substantially reduce the incidence of myocardial infarction, stroke, revascularization, and cardiovascular death in primary prevention of cardiovascular disease. These benefits were shown to be consistent irrespective of cardiometabolic risk factors. The combination pills, or polypills, included ≥2 blood pressure-lowering agents plus a statin, with or without aspirin.[7] If applied to all the people who live in low and middle-income countries, there would be a dramatic decrease in cardiovascular-related morbidity and mortality, since most people with undiagnosed or uncontrolled hypertension live in those countries.[2]

Note: Calcium channel blockers of the non-dihydropyridine variety must **not** be administered in combination with beta-blockers as they may promote bradycardia or an atrioventricular block (AV block)!

Depending on the individual comorbidities, the respective medications may either gain or lose significance. **A popular question in exams pertains to the following combinations:** In case of hypertension combined with heart failure, diuretics are an option. ACE inhibitors may be used if there is heart failure, diabetic nephropathy. Beta-blockers are also used for the treatment of heart failure.

When choosing individual medications, side effects, individual tolerance, and interaction with other medications must be considered. If a two-drug combination is not effective, a

third drug may be added.

Isolated systolic hypertension should be treated the same way as systolic and diastolic hypertension. However, since ISH occurs mostly in older patients, BP reduction should always be gradual (over 3–6 months) in these patients. Ideally, maximal emphasis should be placed on nonpharmacologic therapy, particularly salt restriction and weight loss in obese patients, because antihypertensive drugs commonly cause orthostatic (postural) and/or postprandial hypotension in older hypertensive patients.

Complications of Uncontrolled Hypertension

- Congestive heart failure, both types: with reduced ejection fraction (systolic), and with preserved ejection fraction (diastolic)
- Ischemic stroke
- Intracerebral hemorrhage
- Left ventricular hypertrophy
- Ischemic heart disease, including angina and myocardial infarction
- Chronic kidney disease and end-stage kidney disease

High-yield fact:

Hypertension is considered the most common cause of ascending aortic aneurysm. On the other hand, atherosclerosis is considered the most common cause of descending aortic aneurysm.

Prevention

Preventive approaches include the elimination or reduction of hypertension risk factors.

Review Questions

1. **How is isolated systolic hypertension treated?**
    A. Not at all
    B. In the same way as systolic and diastolic hypertension
    C. With beta blockers only
    D. With ACE inhibitors only
    E. With diuretics only
2. **What are not first-line antihypertensive medications?**
    A. Calcium channel blockers
    B. ACE inhibitors
    C. Alpha-1 receptor blockers
    D. Angiotensin receptor blockers
    E. Diuretics
3. **Which of the following laboratory parameters must be determined first when first diagnosing hypertension?**
    A. AST
    B. CRP
    C. eGFR
    D. ESR
    E. GPT

Answers: 1B, 2C, 3C

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