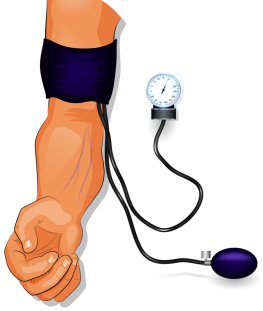


Hypertension

INTRODUCTION

Hypertension (HTN or HT), also known as high blood pressure or arterial hypertension, is a chronic medical condition which refers to persistent elevation of arterial blood pressure. Hypertension is a major risk factor for myocardial infarction (MI), stroke and chronic kidney disease (CKD). Most cases of hypertension are essential (primary), however in some cases there may be a secondary cause(s) or contributory factor. Hypertension is typically asymptomatic (known as a silent killer). However, signs and symptoms may reflect underlying end-organ damage or a potential secondary cause.

Hypertension Mechanisms

1. Primary hypertension: stems from an unknown etiology (no identifiable cause) is the result of 90-95% of cases.
2. Secondary hypertension: stems from many causes which include kidney disease, renovascular disease, medications, endocrine related issues and many more.

RISK FACTORS

- Family history or premature CVD
- Excess alcohol intake
- Smoking
- Excessive salt intake in the diet
- Medical conditions:
  - Dyslipidemia, heart disease, kidney disease
- Obesity and lack of physical activity
- Licorice root

CLINICAL PRESENTATION

- Primary hypertension: asymptomatic
- Secondary hypertension: symptoms are related to the underlying condition causing the elevated BP

Blood Pressure Targets:

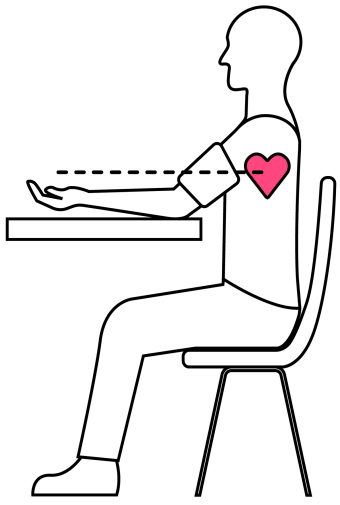
General target: < 140/90 mmHg
Diabetic patients target: < 130/80mmHg

BLOOD PRESSURE MONITORING

Blood pressure is measured using a sphygmomanometer.

WHAT TO DO:	WHAT NOT TO DO:
• Empty the bladder by going to the washroom • Sit on a chair with both feet placed on the floor and relax for at least 5 minutes • Use the correct cuff size • Support the arm at heart level (e.g. resting on a desk) • Wait 1-2 minutes in between measurements	• Talk • Sit or lie down on an examination table • Consume caffeine, exercise or smoke within 30 minutes prior

Be aware of "white coat effect" which is elevated BP in doctor's office



Compensatory mechanism in hypertension

Angiotensinogen (released from liver)

Sympathetic Nervous System

Aliskiren

-

Renin (released from kidneys)

Alpha-2 agonists

-

Angiotensin I

ACE inhibitors

-

ACE

Angiotensin II

Norepinephrine

Aldosterone antagonists

AT_1 receptors

-

Beta-blockers (depending on selectivity)

-

Aldosterone secretion

Vasoconstriction

a-1 receptors

-

ARBs

beta-1 receptors

Thiazide diuretics

-

Increased sodium reabsorption and water retention

Increased SVR

Increased HR and contractility

-

DHP CCBs

-

Non-DHP CCBs

Increased Blood Pressure

BP = SVR x cardiac output (CO)

CO = stroke volume x HR

TREATMENT

SELF-CARE MEASURES

1. Weight reduction (target BMI: 18.5-24.9)
2. Adopt the DASH diet; high fruit and vegetable intake, low fat dairy and low in saturated fats and smoking cessation
3. Limit sodium intake to under 2000mg/day
4. Physical activity for 30-60 minutes/day on 4+ days of the week
5. Limit alcohol intake (< 14 drinks/week for men and < 9 drinks/week for women)

Lifestyle modifications can reduce BP well over 20 mmHg

PHARMACOLOGICAL MANAGEMENT

- **See algorithm below**
- If the average SBP/DBP is ≥ 160/100 mm Hg, pharmacologic treatment is recommended in addition to self-care measures
- If the average SBP/DBP is 140–159/90–99 mm Hg, drug treatment is recommended only IF the patient has:
  - Hypertensive target organ damage or
  - Other risk factors for cardiovascular disease such as: smoker, dyslipidemia, family history, obesity, sedentary lifestyle, males > 55 years of age, females > 60 years of age
- Generally, patients should be reassessed every 4-8 weeks for dose titrations.
- Pregnancy
  - All pregnant women with hypertension should receive aspirin 81 mg daily as well as 1 g of calcium supplementation regardless of dietary intake.
  - 1st line therapy for uncomplicated hypertension:
    - Methyldopa, labetalol, nifedipine XL.
    - Other medications safe to use in pregnancy and are considered alternatives:
    - Clonidine, other beta blockers (except atenolol)
      - Atenolol should be avoided in pregnancy (fetal intrauterine growth restriction).

Abrupt clonidine withdrawal / MAOIs can cause hypertensive emergency → treated with felodipine.

Patients on 3 or more medications with uncontrolled BP are classified as having resistant hypertension

Hypertension (algorithm 1)

Uncomplicated Hypertension

1st line therapy, select one of the following agents:

- Diuretic
- Beta-blocker
- ACEI
- ARB
- CCB

Patient characteristics will help guide the selection

2nd line therapy:
Use a combination of any 1st line options based on patient characteristics

Hypertension + other indications (see algorithm 2 below)

Guidance on selection of proper 1st line therapy based on patient characteristics:

- **Diuretics:** use 1st in elderly or black patients.
- **Beta blockers:** use 1st in young patients (under 60 years old) or those with CV conditions (angina, past MI, or heart failure).
- **ACEI/ARB:** use 1st in non-black patients, and those with diabetes, CKD, ischemic heart disease, history of MI or heart failure.
- **CCB:** use 1st in elderly and black patients.

Hypertension (algorithm 2)

Condition	1st line	2nd line
Diabetes (DM)	ACEI or ARB	Add DHP-CCB
DM with renal, CVD, cardiovascular risks or albuminuria	ACEI, ARB, DHP-CCB, thiazide diuretic	Combine 2 options *ACEI + DHP-CCB preferred over ACEI + thiazide diuretic
Left ventricular hypertrophy	ACEI, ARB, CCB or thiazide diuretic	Add other 1st line options
Nondiabetic chronic kidney disease with proteinuria	ACEI (ARB alternative to ACEI), consider adding diuretic to control	Add other 1st line options
Coronary artery disease	ACEI or ARB; BB or CCB if stable angina	DHP-CCB
History MI (recent)	BB + ACEI (ARB alternative to ACEI)	DHP-CCB
History of Stroke or TIA	ACEI + thiazide diuretic	Add other 1st line options
Heart failure	BB + ACEI (ARB alternative to ACEI)	Consider the following: • Adding ARB to ACEI • Adding a thiazide or loop diuretic • Hydralazine/isosorbide dinitrate combination if ACEI/ARB cannot be tolerated or black ethnicity • DHP-CCB (not nifedipine) • Use angiotensin receptor-neprilysin inhibitor (ARNI) instead of ACE inhibitor or ARB if symptoms unresolved

Table 1: Cardiovascular disease drug chart

Drug Class & Agent(s)	Important Clinical Information
Angiotensin Converting Enzyme Inhibitors (ACE inhibitors, ACEI) **MOA:** Prevents angiotensin I from becoming angiotensin II by formation of an enzyme – inhibitor complex. - Benazepril - Captopril - Cilazapril - Enalapril - Fosinoprol - Lisinopril - Perindopril - Quinapril - Ramipril - Trandolapril	**Side effects**: dry hacking cough, hyperkalemia, renal failure (in susceptible patients), dizziness. **Rare adverse effects**: angioedema. Coughing is an inconvenience to the patients, and it is the main reason patients are switched from ACEI to ARB, who act very similarly but don't have this side effect. **Monitoring**: BP, potassium levels, renal function, ACEI may increase lithium levels (monitor). Contraindicated in pregnancy or a history of angioedema. Avoid ACEI and ARBs in patients with hypertension + bilateral renal artery stenosis. *Considered 1st line therapy for non-black patients with uncomplicated hypertension, patients with other medical conditions (diabetes, CKD, ischemic heart disease, history of MI or heart failure).* Common Interactions: • Diuretics + ACEI can cause increased hypotensive effect • K-sparing diuretics + ACEI can cause hyperkalemia which can lead to a heart block • Lithium + ACEI (avoided) - ACEI can increase lithium retention • Capsaicin + ACEI can cause increased coughing • Indomethacin + ACEI can cause reduced hypotensive effect • Phenothiazines + ACEI can cause increased hypotensive effect • Rifampin + ACEI can cause increased hypotensive effect by altering liver clearance
Angiotensin II Receptor Blockers (ARB) **MOA:** Angiotensin II is a vasoconstrictor. ARB acts to block this blocks vasoconstriction and aldosterone from being released. - Candesartan - Eprosartan - Azilsartan - Irbesartan	**Side effects**: similar to ACE inhibitors but with less cough/angioedema. • They are considered a good alternative to ACEI to those who can't tolerate ACEI due to the cough. *Considered 1st line therapy for uncomplicated hypertension as well as in patients with diabetes or ischemic heart disease.* *Note: losartan may be a suitable agent for management of hypertension in patients with gout.*

- Losartan - Olmesartan - Telmisartan - Valsartan	
Direct Renin inhibitors **MOA:** Acts directly on renin, and inhibits it from converting angiotensinogen to angiotensin I. - Aliskiren	**Side effects**: hyperkalemia, diarrhea, possible dry cough. *Grapefruit may lower concentrations.* **Avoid using with ACEI and ARB.** Contraindicated in pregnancy. Interactions: aliskiren is a major substrate of P-gp.
Beta Adrenergic Blockers (beta blockers, BB) **MOA:** Competitively block beta 1 +/- beta 2 adrenergic receptors result in decreased HR and myocardial contractility. **Non-selective BB:** - Nadolol - Propranolol - Timolol **Beta$_1$-selective BB:** - Atenolol - Bisoprolol - Metoprolol - Nebivolol **Non-selective BB with alpha$_1$ blocking activity:** - Labetalol - Carvedilol (not used in treatment of hypertension)	**Side effects**: bradycardia, headache, impotence, vivid dreams, fatigue and depression. **Caution**: serious side effects (not common) include masking symptoms of hypoglycemia, worsen hyperglycemia and hypoglycemia, heart block, heart failure, caution in patients with bronchospastic disease (COPD/asthma), masking symptoms of hyperthyroidism. ▪ Non-selective beta blockers should be avoided in patients with asthma or other respiratory disorders. Beta$_1$-selective BB are selective to the heart, and thus have less non-cardiac side effects and are preferred in asthma. **Contraindications**: use in patients with 2nd or 3rd degree heart block and should be avoided in those with peripheral artery disease. **Warning**: when stopping beta blocker therapy, taper the dose off slowly and avoid abrupt discontinuation as abrupt withdrawal can cause rebound hypertension and ischemia. Note: beta blockers that have intrinsic sympathomimetic activity (ISA) include **acebutolol and pindolol**. These agents stimulate beta receptors while blocking catecholamines (i.e. norepinephrine), these agents do not reduce the heart rate to the same extent as beta blockers without ISA – are thus not recommended in post MI patients. **Propranolol** has the greatest lipid solubility among the BB. It can readily penetrate the CNS and cause CNS side effects (insomnia, vivid dreams) more so than other agents. **Labetalol** has additional alpha blocking properties. Additional side effects associated with labetalol include edema, nasal congestion and postural hypotension.

	Interactions: • Carvedilol, propranolol and metoprolol all major substrates and nebivolol is a minor substrate of CYP2D6. • Propranolol and carvedilol are inhibitors of P-gp which increase concentrations of common P-gp substrates such as digoxin, dabigatran and cyclosporine.

Calcium Channel Blockers (CCB)
 	
MOA: Inhibits calcium ion from entering slow channels to produce relaxation of coronary smooth muscle and coronary vasodilation.
 	
Dihydropyridine:
- Amlodipine
- Felodipine
- Nifedipine
- Nimodipine (only used for subarachnoid hemorrhage)
 	
Non-dihydropyridine:
- Diltiazem
- Verapamil
	Side effects:
	• **Dihydropyridine:** flushing, headaches, peripheral edema, tachycardia, gingival hyperplasia, dizziness and fatigue.
	• **Non-dihydropyridine:** bradycardia, heart block, heart failure, headache, constipation (verapamil).
	
	Monitoring:
	• **Dihydropyridine:** BP and peripheral edema.
	• **Non-dihydropyridine:** BP, ECG, LFTs.
	
	Contraindications:
	• Nifedipine, diltiazem and verapamil in patients with severe hypotension or cardiogenic shock.
	• Verapamil and diltiazem in post MI patients with ejection fraction under 40%, patients with 2nd or 3rd degree heart block.
	• Long acting formulations of nifedipine in patients with GI obstruction conditions
	
	Interactions:
	• Grapefruit juice may elevate serum concentrations of all CCBs (avoid) *especially felodipine.
	• All CCBs are major substrates of CYP3A4
	  ○ Potent inhibitors include ritonavir, azole antifungals, macrolides and quinidine.
	  ○ Potent inducers include phenobarbital, phenytoin, rifampicin, and St. John's Wort.
	• Patients receiving diltiazem / verapamil are exposed to increased negative chronotropic effect with beta-blockers, digoxin and amiodarone.
	  ○ Monitor digoxin levels as verapamil may cause 50-70% increase in serum digoxin concentrations.
	  ○ Patients receiving statins while taking diltiazem / verapamil should use a statin that is not metabolized by CYP3A4 such as pravastatin / rosuvastatin or use lower dose of simvastatin / lovastatin (simvastatin and lovastatin are metabolized by CYP3A4).
	  ○ Avoid using diltiazem / verapamil with ivabradine.
	
	Note:
	➢ non-DPH CCBs (**verapamil and diltiazem**) are more selective for the myocardium compared to DHP-CCBs. These agents reduce BP through **negative inotropic** (reduced ventricular contraction force) and **negative**

	chronotropic (reduced heart rate) effects. ➢ Only use long acting formulation of CCB in the management of hypertension. Trials have shown that short acting CCB can have negative effects on the patients, including increased risk of experiencing a CV event. ➢ Short acting nifedipine should be avoided as they have caused increased CVD events in RCTs. ➢ Increased negative chronotropic effect with beta-blockers, digoxin, amiodarone.
Potassium Sparing Diuretics **MOA:** Increases salt and water excretion. Conserves potassium and hydrogen ions. - Spironolactone - Amiloride - Triamterene - Eplerenone	**Side effects**: diarrhea, fatigue, headaches, hair loss, nausea/vomiting, abdominal cramps. • Spironolactone side effects: gynecomastia in men and breast tenderness in women. • Eplerenone: hypertriglyceridemia. Monitoring: BP, electrolytes (potassium levels), renal function, fluid status. Note: avoid potassium supplements, foods/salts (e.g. bananas, prunes and orange juice). ➢ *Triamterene can turn urine blue and is harmless.*
Thiazide Diuretics **MOA:** Inhibits sodium reabsorption in the distal tubules. & Increases sodium, water, potassium, and hydrogen ion excretion. - Chlorthalidone - Hydrochlorothiazide (HCTZ) - Indapamide - Metolazone	**Side effects**: hypotension and lab abnormalities (hypokalemia, hypomagnesemia hyponatremia, hyperuricemia, hyperglycemia, hyperlipidemia), rash, dizziness, photosensitivity, muscle cramps **Contraindications**: hypersensitivity to sulfonamide-derived drugs (unlikely to cross-react). **Monitoring**: lab values, especially Scr and K levels, diuretics may increase lithium levels [monitor]. **Renal**: avoid use in patients with CrCl <30 mL/min., as they are not effective when poor renal function is present. Exception = metolazone, can be used. **Interactions**: avoid drugs that may result in sodium/water retention (i.e. NSAIDs) since they reduce the effective of antihypertensives. Notes: may exacerbate gout (due to hyperuricemia) and diabetes (due to hyperglycemia). Use with caution and monitor in those patients. ➢ Remind patients to take in the morning in order to avoid nocturia.
Centrally Acting Agents MOA: Stimulate central alpha-adrenergic receptors in order to decrease sympathetic outflow.	**Side effects**: dry mouth, fatigue, dizziness, constipation, headache, behavioural changes. Drugs in this class include methyldopa and clonidine

Alpha Adrenergic Antagonists MOA: Inhibits postsynaptic alpha 1 receptors leading to vasodilation and lowers the amount of peripheral resistance. - Doxazosin - Prazosin - Terazosin	**Side effects**: orthostatic hypotension, syncope, drowsiness, palpitations. Start with lower dose and titrate slowly to avoid syncope. Advise patients to get up from a sitting position slowly and make sure they support themselves (e.g. on the wall). *Not considered 1st line agents.* See BPH chapter for more information on this class of medication.