

# Drug Therapy of Hypertension

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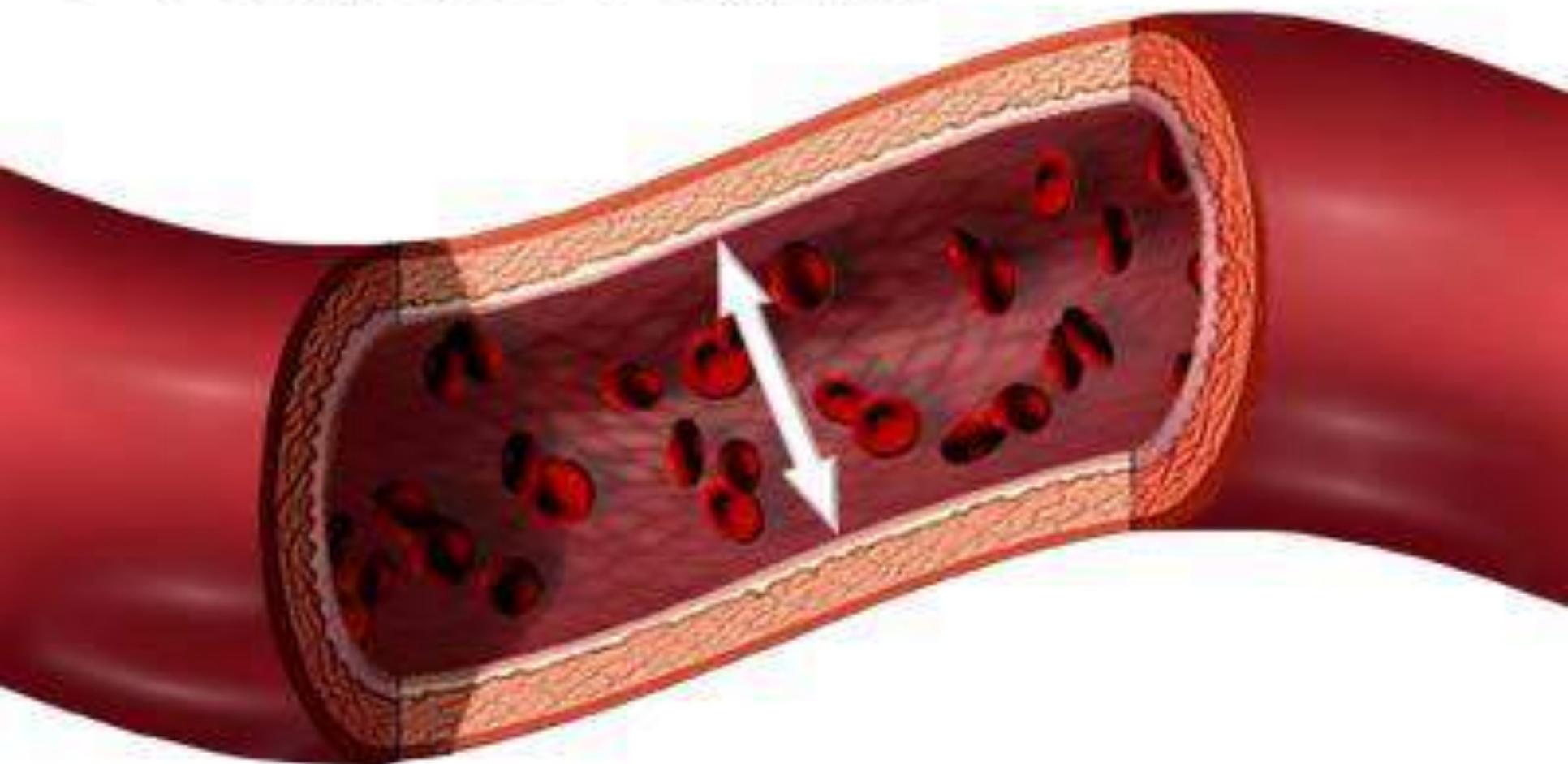


- Normal ABP= or  $< 120/80$  mmHg
- Pre-hypertension:  $120 - 140/80 - 90$  mmHg
- Hypertension= or  $> 140/90$  mmHg
- Stage 1=  $140-160/ 90-100$  mmHg (Mild)
- Stage 2 =  $>160 / 100$  mmHg (Moderate)
- Stage 3 =  $> 180/110$  mmHg (Sever)

# Diagnosis

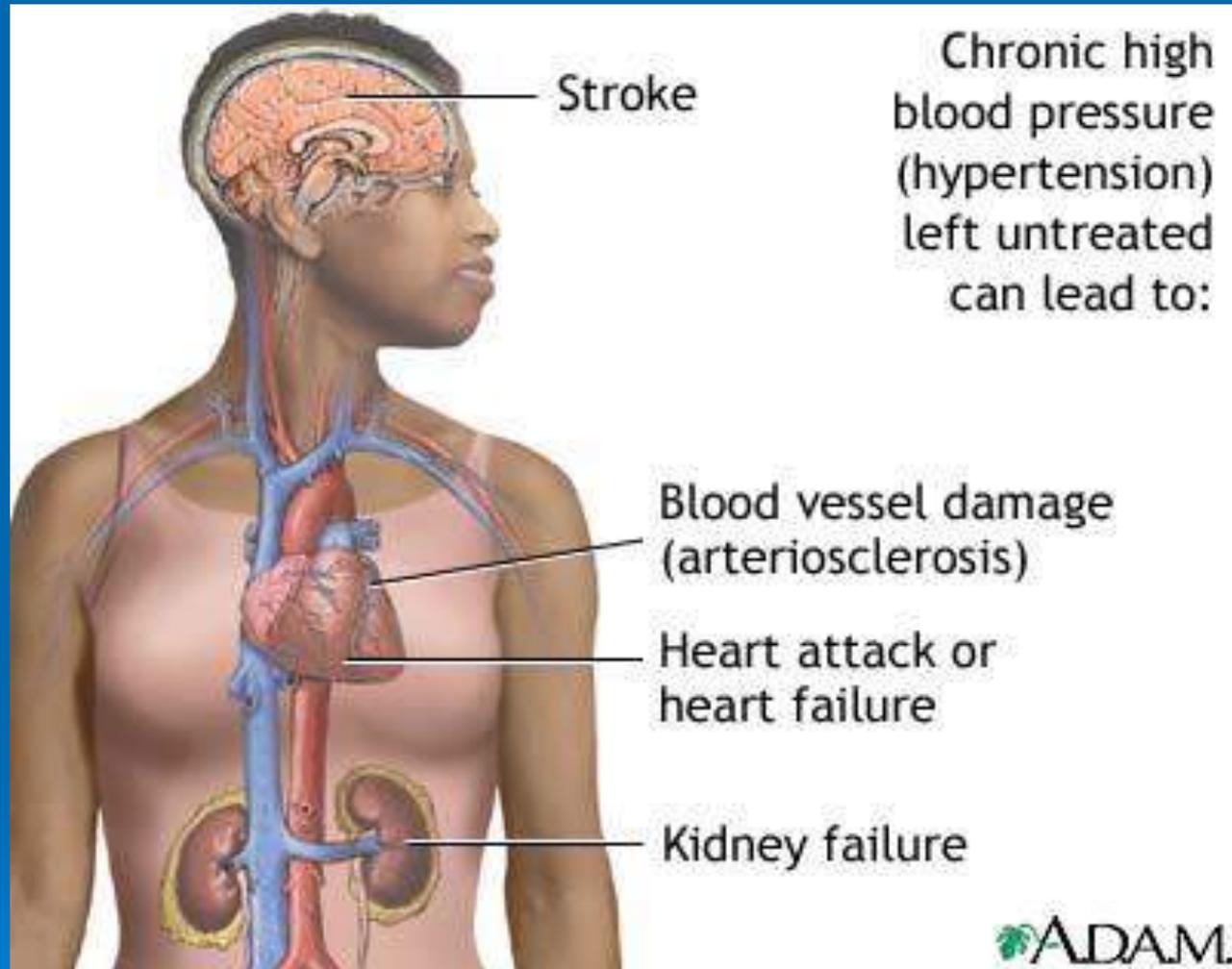
- Hypertension (HTN) is defined as a persistent blood pressure **equal to or more than 140/90 mm Hg**
- Assessment of vital functions e.g. heart , kidneys & retina
- Presence of complications encephalopathy, renal & heart damage
- Whether HTN is essential (primary) or secondary

Blood pressure is the measurement of force applied to artery walls



# General Considerations

- Aim of therapy is to **reduce ABP** back to normal (<140/90 mm Hg)
- Duration of **treatment** is usually **life-long**
- Benefits of treatment are to **reduce complications** CVA, heart failure, renal failure & MI
- **Precautions** in advanced renal, coronary & cerebral disease & in elderly not to lower ABP rapidly nor to a very low level



# Etiology

90% essential hypertension

(Primary or Idiopathic)

10 % Secondary hypertension

(Kidney diseases, Renal artery stenosis)

Endocrine diseases (Pheochromocytoma,  
Cushing's disease & Conn's syndrome)

Toxemia of pregnancy

Drugs (OCP, Corticosteroids)

- HTN is a multifactorial problem, genetic, environmental (Stress, Obesity, smoking), dietary (High intake of Na)
- HTN is associated with an increase in the peripheral vascular resistance secondary to increased intra-cellular Na and consequently intracellular Ca.

- Screening of hypertension is important to detect early asymptomatic patients.
- It occurs more often among middle age males.
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# Benefits and precautions

- The benefit of treatment is due to reduced complications as :- CVA, Heart Failure, MI & renal failure.
- Precaution in elderly patients & with advance renal, coronary and cerebral disease caution is required during therapy
- Rapid lowering of ABP or lowering to a very low level is to be avoided.

# Lines of Treatment

## ➤ General measures:

- Weight reduction
- Stoppage of smoking & alcohol
- Avoidance of extra salt
- Control of hyper-lipidaemia
- Good balanced healthy diet that include
  - Avoid extra salt intake
  - Increasing K and Ca intake
  - Low fat contain with more fruit and vegetables.

# Lines of treatment

- Drug therapy using agents acting on one or more of the factors that determine BP including:-
  - Cardiac output
  - Peripheral vascular resistance
  - Blood volume.
  - Blood viscosity.

# Therapeutic strategies

- Mild HTN can often be controlled with a single drug (Mono-therapy)
- Initiate therapy with a thiazide diuretics unless contraindicated.
- If ABP is uncontrolled, a second drug should added (Combination therapy)
- Usually Beta-blockers is added to thiazide or Thiazide is added when a beta-blockers is used initially
- Triple therapy by adding a vasodilator to the double therapy (For patient not responding).



# Therapeutic strategies

## ➤ First line drugs:-

- Beta-blockers, Thiazide diuretics, ACE inhibitors and Ca antagonists.
- Ca antagonist, ACEI and diuretics are favored in treatment of HTN in elderly patients.
- Beta-blockers are preferred in hypertensive patients with coronary artery diseases.
- Patients with chronic renal disease respond better to ACEI

# Antihypertensive Groups

- 1. Diuretic which lower ABP by reducing Na in the body and so reducing Blood volume.
- 2. Sympathoplegic drugs which reduces ABP by reducing PVR & depressing cardiac function
- 3. Vasodilators which reduces ABP by reducing the PVR and by vasodilatation
- 4. Inhibitor of angiotensine including drugs that inhibit production or actions of the angiotensine and so reduces the PVR and blood volume.



Exercise and maintenance of a healthy weight

Lifestyle changes and/or medication may reduce high blood pressure to healthy levels:

Medications such as diuretics, beta-blockers, potassium replacements, calcium channel blockers and ACE inhibitors

A healthy, low-fat diet rich in natural sources of vitamins and minerals



 ADAM.

# Classes of Antihypertensive Drugs

1. Diuretics
2. Beta-blocker
3. ACEI
4. Angiotensine II receptor antagonists
5. Ca channel blockers
6. Alpha adrenoceptor blockers
7. Centrally acting adrenergic drugs
8. Vasodilators.

# Diuretics

- Increases the secretion of Water & electrolytes by the kidneys
- Initially reduces the blood volume and Cardiac output & later reduces the PVR
- Recommended as the first line of therapy in HTN unless contraindicated.
- Alone, they are useful treatment for mild and moderate HTN
- In more severe HTN they can be combined with other drugs
- Low dose diuretic therapy is safe and effective and is preferred in elderly over Beta-blockers

# Classification of diuretics

- 1. Thiazide diuretics ( Hydro-chlor-thiazide)
- 2. Loop diuretics (Frusemide)
- 3. K sparing (Spironolactone)

# Thiazide diuretics

- They are moderate efficacy diuretics
- Most commonly used diuretics:
  - Hydrochlorothiazide, bendrofluazide

Can be used alone or in combination with other diuretics or drugs from other class like a beta-blockers.

They inhibit Na re-absorption in the distal tubules leading to increase Na and water excretion.

They reduces ABP due to reduction in the Intra-vascular volume.

# Pharmacokinetics

- Onsite of action is within 1-2 hours after oral administration
- Most have duration of action of 12-24 hours
- They compete with uric acid for renal secretion system thus block its secretion causing hyper-uricaemia.

# Thiazide diuretics

- **Adverse effects:**
- hyperglycaemia, hypokalemia, increase plasma cholesterol, rash & thrombocytopenia, hypo-natremia

# Loop Diuretics: **Furosemide** **Bumetanide**

- Is a high efficacy potent loop diuretics
- Acts on the ascending limb of loop of Henle
- It is indicated in Sever HTN associated with renal failure, oedema, and cardiac failure.
- It is not indicated in routine daily treatment of HTN because of its high potency

# Pharmacokinetics

- - Given orally and parenterally
- - Is eliminated by the kidneys
- - Onset of action within 1 H after oral administration.
- - they are used usually once daily in the morning (or twice if necessary)

# Pharmacodynamics

- Most potent diuretics
- They increase Ca excretion in urine
- Frusemide has vasodilator effect and reduces PVR and cardiac work

# Adverse effects:

- Hypovolemia
- Hypokalemia
- Hyponatremia
- Hyper-uricemia

# K sparing diuretics

- Is a **low efficacy K-sparing** diuretic
- Acts on **distal tubules**
- Spironolactone amiloride & triamterene
- It is effective in hypertension associated with hypokalemia and in Heart failure.
- **Effective** in Conn's syndrome & HTN associated with hypokalemia
- **Adverse effects:** hyperkalemia, gynecomastia & impotence

# K sparing diuretics

- It is structurally similar to aldosterone & acts as a competitive aldosterone antagonist
- Aldosterone causes Na re-absorption and K excretion by the kidney
- Causes Na excretion and K retention

# K sparing diuretics

- Given only orally
- Onset of Action is slow & may require several days before full therapeutic effect is achieved.
- Pharmacodynamics:-
  - - Increase urinary excretion of Na and water and decrease excretion of K

# Adverse effects

- HyperKalemia
- Gynecomastia & impotence
- Gastric upset & peptic ulcer
- Spironolactone is contra-indicated in renal failure because of the risk of hyperkalemia

## 2. Beta-blockers

- They reduces the BP by decreasing cardiac output & inhibit renin release from kidney

## 2. Beta-blockers

- **Atenolol** & Metoprolol are a **cardioselective beta-blocker** used **once daily**
- **Propranolol** is a **non-selective blocker**
- They are very useful in hypertensive patient with concomitant diseases, **MI, angina and migraine headache**
- They are **contraindicated** in heart failure, asthma, heart block, diabetes mellitus & in peripheral vascular disease

# 3. ACE inhibitors

- Captopril (capoten), Enalapril & Lisinopril
- They **block angiotensin converting enzyme (ACE)** that converts angiotensin I into angiotensin II
  - Angiotensin II is a potent vasoconstrictor & stimulates aldosterone production from adrenal cortex leading to Na & water retention
  - Useful in hypertension particularly
    - chronic renal disease
    - Left ventricular hypertrophy

# 3. ACE inhibitors

- Captopril is given twice daily
- Enalapril is prodrug is given once daily
- Adverse effects:
  - dry cough
  - loss of taste sensation
  - increase blood potassium
  - stomatitis, abdominal pain

They are contr-indicated during pregnancy

# 4 Angiotensine II receptor antagonists

## ➤ Losartan & Candesartan

They are angiotensine II receptor blockers

They produce vasodilatation & block Aldosteron secretion

Given once daily in HTN particularly when patients on ACEI developed cough

They are also useful in Hypertensive patients with diabetes.

# 4. Ca Antagonists

- Nifedipine, Verapamil, Diltiazem & amlodipine
- Act by inhibiting influx of Ca (Ca channel blockers)
- This lead to decrease intracellular Ca & vascular smooth muscle relaxation & a direct –ve inotropic effect
- They are potent vasodilator of arterial side

# 4. Ca Antagonists

- **Direct action on heart** (-ve chronotropic & inotropic effects) with **verapamil**
- They are **safe** in renal disease
- **Adverse effects:** headache, flushing, increase heart rate (nifedipine), decrease heart rate (verapamil) & ankle oedema

# 5. Angiotensin II receptor antagonists

- **Losartan**
- They produce **vasodilatation & block aldosterone secretion**
- Given **once daily** in HTN particularly when patients on **ACEI develop cough**
- It is also useful in **heart failure**

# 6. Vasodilators

## ➤ Nitroprusside:

- A potent vasodilator of venous & arteriolar sides
- Its  $t_{1/2}$  is few minutes, should be given by continuous IV infusion
- It is indicated in **complicated hypertensive crisis** (associated with LVF, encephalopathy & dissecting aneurysm)
- **Adverse effects:** excessive hypotension, sweating & palpitation

# Hydralazine (Apresoline)

- Is a **direct arterial vasodilator** that reduces BP by reducing PVR
- **Na & water retention** may occur leading to oedema
- **Tolerance** to hypertensive effect may occur if it **used alone**
- It is used **with beta-blockers & diuretics**
- It is used in **pregnancy-induced HTN**

# Minoxidil

- It is **very potent vasodilator**
- Should be used for treatment of **severe HTN** resistant to other drugs
- It causes **Na & water retention**
- It must be prescribed **with a beta-blocker & a diuretic**
- **Adverse effects:** hypertrichosis

# 7. Alpha-adrenoceptor Blocking Drugs

- Prazosin, doxazosin & terazosin
- Produce a **competitive block of alpha 1 receptor**
- They decrease PVR & BP by causing **relaxation of both arterial & venous smooth muscle**
- Alpha blockers **improves flow of urine** in patients with **benign prostatic hypertrophy**

# 8. Centrally Acting Antihypertensives

## ➤ **Methyldopa** (Aldomet):

- This reduces PVR leading to hypotensive effect
- Is indicated in HTN associated with **asthma, HF, pregnancy & DM**

# Hypertension During Pregnancy

## ➤ Useful drugs include:

- Methyldopa
- atenolol (or labetalol)
- hydralazine

# Hypertensive Emergencies

- **Oral therapy** e.g. Thiazide + beta-blocker  
Vasodilator + beta-blocker  
Thiazide + methyldopa
- **Parenteral therapy** is indicated in presence of complications ( LVF, dissecting anuresym, eclampsia & encephalopathy) includes nitroprusside, diazoxide, labetalol & methyldopa