Drug Therapy of Hypertension

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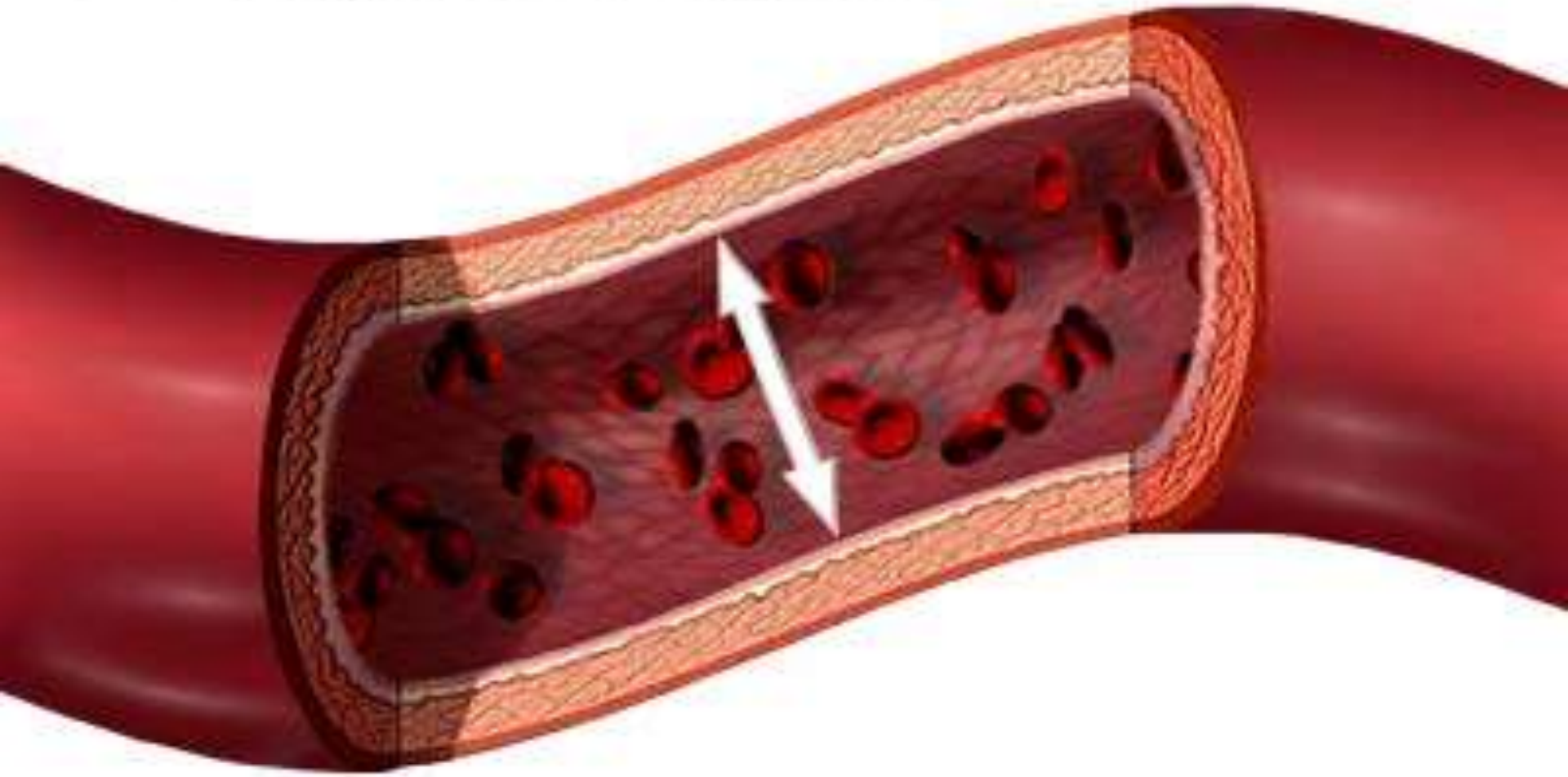
- Normal ABP= or < 120/80 mmHg
- Pre-hypertension:120 – 140/80 – 90 mmHg
- Hypertension= or > 140/90 mmHg
- Stage 1= 140-160/ 90-100 mmHg (Mild)
- Stage 2 = >160 / 100 mmHg (Moderate)
- Stage 3 = > 180/110 mmHg (Sever)

Diagnosis

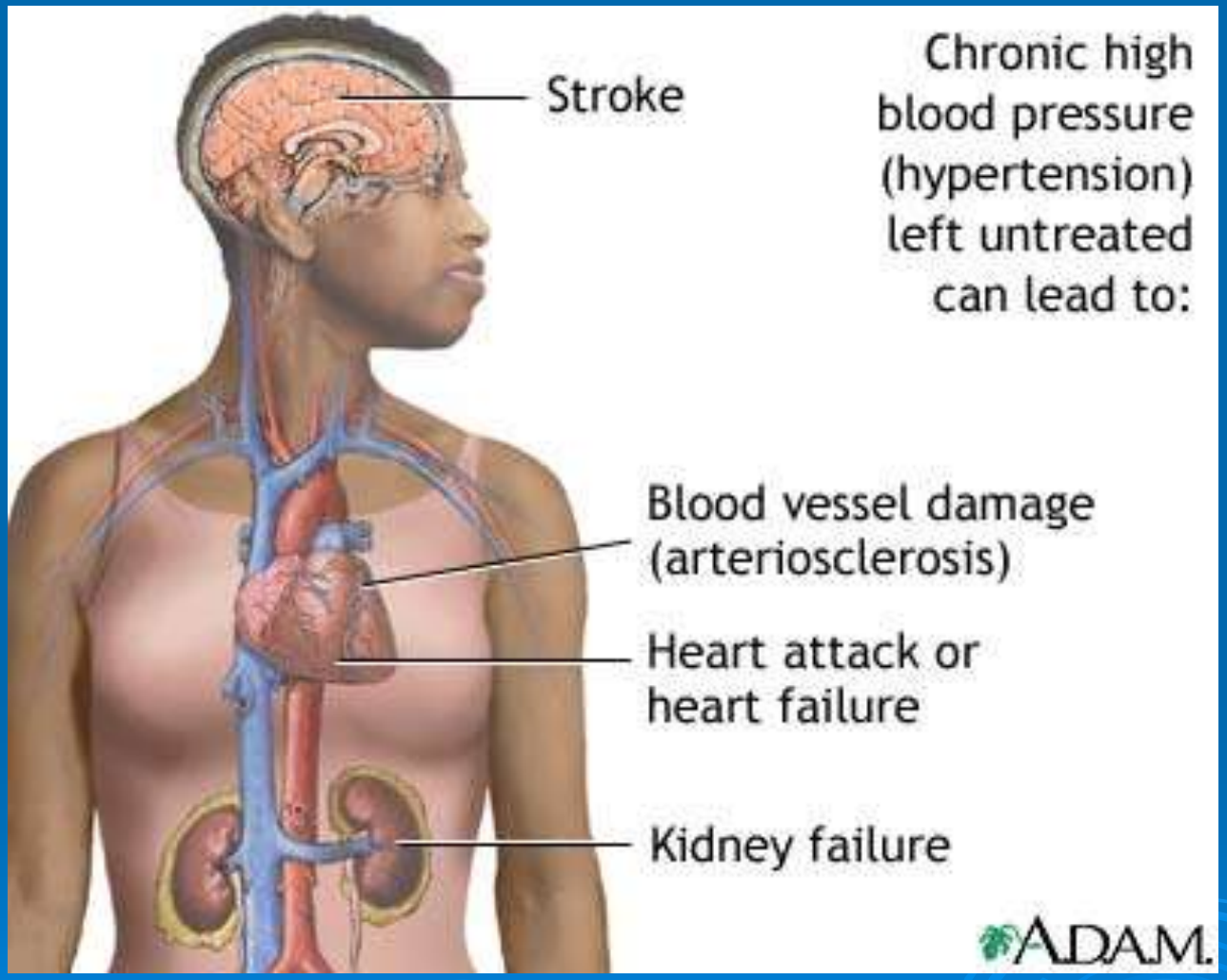
- Hypertension (HTN) is defined as a persistent blood pressure **equal to or more** than **140/90 mm Hg**
- Assessment of vital functions e.g. heart , kidneys & retina
- Presence of complications encephalopathy, renal & heart damage
- Whether HTN is essential (primary) or secondary

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


Chronic high blood pressure (hypertension) left untreated can lead to:
Stroke
Blood vessel damage (arteriosclerosis)
Heart attack or heart failure
Kidney failure
A.D.A.M.

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 controled 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).
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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 redusing 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

A.D.A.M.

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 contrindicated.
- Alone, they are useful treatment for mild and moderate HTN
- In more sever HTN they can be combined with other drugs
- Low dose diuretic therapy is save 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:

  - Hydrochlorthiazide, 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: Frusemide 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 hypertenssion 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 milletus & 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, Dlitiazem & 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 ½ is few minutes, should be given by continuous IV infusion
- It is indicated in **complicated hypertensive** crisis (associated with LVF, encephalopathy & dissecting aneurysem)
- **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