Antihypertensive

Blood pressure is equal to or above 120/ 80 mm of Hg after measuring at least on three different occasions in supine and standing position after giving proper rest to the patient.

Grade	Diastolic blood pressure
MILD	90-104
MODERATE	105 – 115
SEVERE	> 115

Grade	Diastolic B.P.	Systolic B.P.
I	90- 100	140 -160
II	100- 110	160- 180
III	110- 120	180 – 210
IV	> 120	> 210

Parameters According to JNC 7

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines/hypertension/phycard.pdf

What is High Blood Pressure?

JNC 7 Guidelines for Patients Age ≥18 Years

BP classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	*and* <80
Prehypertension	120–139	*or* 80–89
Stage 1 hypertension	140–159	*or* 90–99
Stage 2 hypertension	≥160	*or* ≥100

JNC, Joint National Committee; DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure.
http://www.nhlbi.nih.gov/guidelines/hypertension/phycard.pdf

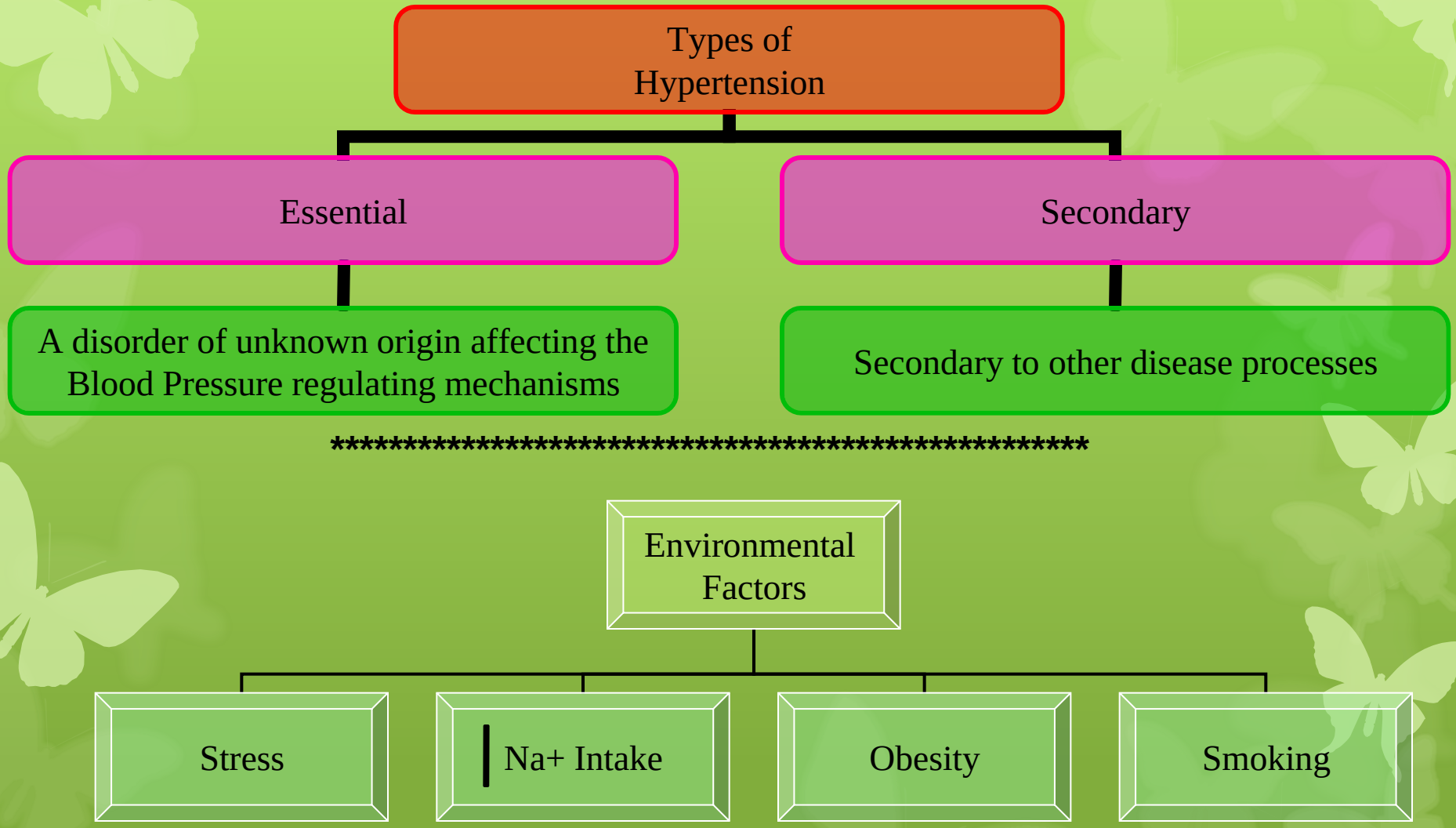
- Normal BP is defined as <120/<80 mm Hg;
- Elevated BP 120-129/<80 mm Hg;
- Hypertension stage 1 is 130-139 or 80-89 mm Hg
- Hypertension stage 2 is ≥140 or ≥90 mm Hg.

Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

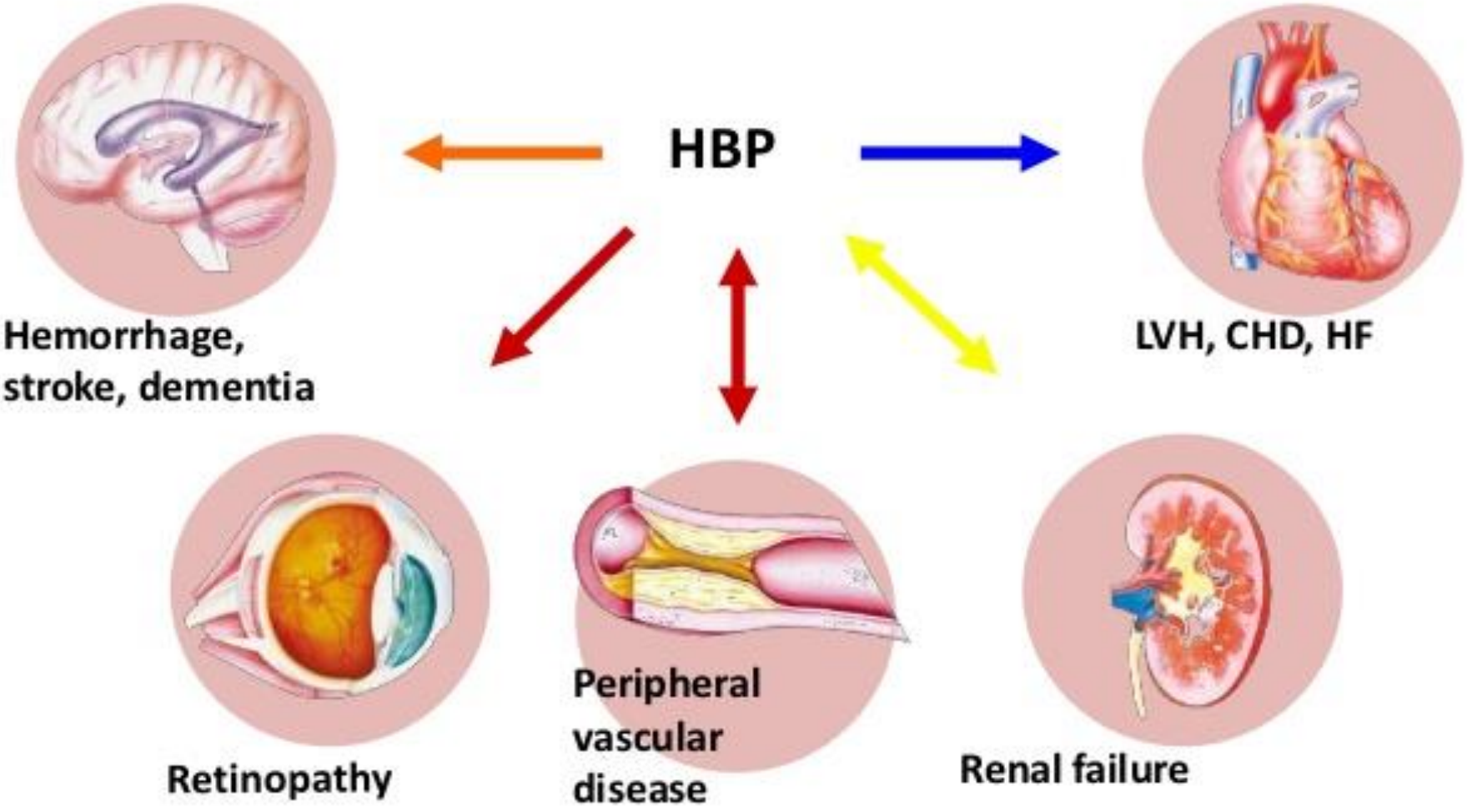

Types of Hypertension
Essential
Secondary
A disorder of unknown origin affecting the Blood Pressure regulating mechanisms
Secondary to other disease processes
****
Environmental Factors
Stress
Na+ Intake
Obesity
Smoking

95 % Cases – Idiopathic / Primary / Essential

5% Cases – Secondary – some identifiable cause .

e.g. Renal disorder
Drug induced
Coarctation of aorta

Blood Pressure >140/90 mm Hg Damages Target Organs



Chobanian AV. *JAMA*. 2003;289:2560-2572.

CHD, coronary heart disease.

Classification of antihypertensive drugs

A Diuretics

1. **Thiazides**

   Hydrochlorothiazide, Chlorthalidone

   Indapamide

2. **Loop diuretics**

   Furosemide

3. **K^+ Sparing**

   Triamterene

   Amiloride

   Spironolactone, Eplerenone

B Sympatholytic

1. **Centrally acting**

a) **Clonidine**

b) **Methyldopa**

2. **β blockers**

   Propranolol

   Atenolol ,Metoprolol

3. **α blockers**

   Prazosin,Doxazosin,Terazosin

   Phenoxybenzamine

4. α +β blockers

Labetalol,Carvedilol

5. Acting on granular uptake of NE- Reserpine

C. Vasodilators

1. Arteriolar

Hydralazine, Minoxidil, Diazoxide

2. Arteriolar + Venous

Sodium nitroprusside

D. Calcium channel blockers

Amlodipine

Nifedipine ,Nicardipine

Verapamil

E. ACE inhibitors

Captopril

Enalapril

Lisinopril

F. Angiotensin II receptor antagonist

Losartan

G. Direct renin inhibitor

Aliskiren

B. P. = C.O X P.R.

Before starting the treatment investigations to be done

- **Haemogram**
- **Urine ®**
- **Blood urea**
- **Blood creatinin**
- **BSL**
- **Lipid profile**
- **Serum electrolytes**
- **ECG**
- **2- D Echo**
- **Fundoscopy**

DIURETICS

Thiazides

1st line drug in treatment of hypertension over period of 25 years .

Mode of action

A.

- **Cause diuresis by inhibiting Na-Cl symporter in early distal convoluted tubule**
- **Prevents Na^+ and Cl reabsorption – excretion**
- **This leads to decrease in ECF**
- **Decrease in blood volume**
- **Decrease in C.O**

Subsequently after 4 - 6 weeks, Na^+ balance and CO is regained by 95%, but BP remains low!

B.

- **They cause decrease in vascular wall stiffness**
- **Decrease sensitivity of vascular bed to catecholamine and angiotesin.**
- **Decrease in peripheral resistance**

Side - effects

Hyponatremia

Hypokalemia – muscle pain and fatigue

Hyperlipidemia -

Hyperuricemia inhibition of uric acid excretion

Hyperglycemia-Inhibition of insulin release due to K^+ depletion (proinsulin to insulin) – precipitation of diabetes

Sudden cardiac death – tosades de pointes (hypokalaemia)

All the above metabolic side effects – higher doses (50 – 100 mg per day)

These adverse effects are minimal with low doses (12.5 to 25 mg)

Dose

JNC recommends low dose of **hydrochlorothiazide** therapy (12.5 – 25 mg per day) in essential hypertension

Cheap. Ca^{++} loss – prevent osteoporosis

K^+ sparing diuretics

Along with thiazides to prevent hypokalemia. They are never used alone as antihypertensive drug

Loop diuretics

Not used routinely

1. **It is high efficacy diuretic so severe electrolyte – volume depletion. Severe k^+ loss**
2. **Short duration of action -4-6 hrs. so it doesn't maintain Na^+ deficient state in vascular smooth muscle round the clock.**

Centrally acting antihypertensive

Clonidine

Mechanism of action

Agonist at α_2 receptors

Mainly acting at central $\alpha_{2\,A}$ ® situated at VMC and hypothalamus

stimulation of $\alpha_{2\,A}$ ® causes decreased release of NE

Decreased sympathetic flow to heart – decreased contractility – C.O – systolic B.P

Decreased vascular resistance – decreased diastolic B.P

Peripheral

α_2 ® situated pre-synaptically on adrenergic never terminals. Clonidine acts on these receptors and decreases the release of NE.

Pharmacokinetics

Oral absorption good

T ½ = 12 hrs.

Never given i. v. – as it will cause sever vasoconstriction by acting at $\alpha_{2\,B}$ receptors on vascular smooth muscle.

Route

Oral, Transdermal

Dose – 0.1 mg BD

Side – effects

- **Sedation – Tolerance develops**
- **Dryness of mouth**
- **Abrupt withdrawal of drug – Rebound HT**
  Tachycardia
  Arrhythmias
- **Sudden removal of inhibition of central sympathetic flow results in release of large quantities of stored NE**
- **Supetrsensitivity of peripheral adrenergic receptors.**
- **Treatment – Substitute clonidine**
  Labetalol ,Sodium nitroprusside.

α Methyldopa

Centrally acting sympatholytic

Mechanism of action

α Methyldopa is converted to α methyl dopamine

↓

α methyl norepinephrine

↓

α_2 agonist

↓

Decrease NE release

Same as clonidine

PK- Oral **safe in Pregnancy**

Prodrug

Side – effects

Sedation – Inhibition of center for wakefulness

Dryness of mouth.

Inhibition of medullary salivary center

Hepatitis

Dose

250 -750 mg BD

Reserpine

Inhibits vesicular uptake of NE.

S/E – Depression. Not used

Inexpensive

Alpha Blockers

Prazosin

Phentolamine

Phenoxybenzamine

Mechanism of action

- **Antagonist at α receptors**
- **Block α_1 receptors situated on vascular smooth muscle of peripheral blood vessels**
- **Effect on arterial resistance is predominant than venous capacitance**
- **Decrease in peripheral resistance**
- **Decrease in B.P.**

S/E

1. **Reflex tachycardia**

Less tachycardia with Prazosin as it is a selective α_1 blocker

2. Postural hypotension

3. 1st dose effect

Prazosin - Syncope d/t excessive reduction in B.P with first dose.

To minimize it-

1) Start the treatment with small dose

2) Drug to be taken at bed- time

With continuation of treatment tolerance develops to it.

Adv - Decreases plasma TG and LDL

Dose

Prazosin – 1 mg TDS

Not used commonly

1. Tolerance to AntiHT effects
2. S/E – Postural hypotension
   Tachycardia

β Blockers

commonly used as antiHT

Mechanism of action

- **Antagonist at β receptors**
- **Block B_1 receptors situated on heart leading to – ve inotropic, chronotropic effect. Decrease in cardiac output and heart rate initial decrease in B.P. is d/t decrease in C.O**
- **Decrease renin release by blocking B_1 receptors on JG apparatus**
- **Initial increase in P.R., with continued use it falls.**
  1 Blockade of presynaptic B_2 receptor
  2 Resistance vessels get adapted to chronic reduction of CO
- **Enhances prostacyclin release / Biosynthesis**
- **Alters baroreceptor sensitivity**

A/E

Bradycardia

Precipitate bronchial asthma

withdrawal – Rebound HT

To be avoided in DM

Increase LDL

Atenolol -50-100 mg OD –Preferred

Not selected as initial antihypertensive

Quality of life –less as compared to ACE inhibitors and calcium channel blockers

Less effective for primary prophylaxis of MI

Prevention of LVH

Calcium channel blockers

Nifedipine Verapamil

Amlodipine Diltiazem

Mecahnism of action

Block 'L' type of voltage gated calcium channels

Cardiac effects.

Block Ca^{++} entry in the cell

-ve inotropic effect

↓

↓ **C.O**

-Ve chronotropic effect

Vascular smooth muscle

Mainly cause arteriolar vasodilatation by blocking Ca^{++} entry

Decrease in P.R.

Amlodipine, Nifedipine – Lack cardiodepressant property

Peripheral vasodilatation activates -Baroreceptor reflex – ↑sympathetic tone

Reflex tachycardia – Less with Nifedipine SR

Amlodipine -Slow, more complete oral absorption

Less reflex tachycardia

Long t ½

Minimal variation in blood con.

Adv.

Can safely be used in

Bronchial asthma

Diabetes mellitus

PVD

No effect on lipid metabolism.

A/ E – Nifedipine – Reflex tachycardia

Palpitations

Ankle edema

Verapamil – Constipation

Precipitate CHF in patients with preexisting disease

Nifedipine S.R. 20 mg, Amlodipine – 2.5, 5, 10 mg

First line drugs-high efficacy, excellent tolerability,

Prevent diabetic/hypertensive nephropathy—next to ACE inhibitors

Vasodilators

Hydralazine

- **Directly act on vascular smooth muscle**
- **Smooth muscle relaxation**
- **Arteriolar dilatation**

↓

Leads to fall in P.R

↓

Decrease in B.P.

Maintains Renal blood flow

Reflex sympathetic stimulation – Tachycardia

Renin –Angiotensin – aldosterone – Na +H_2O Retention

These two mechanism lead to tolerance to hypotensive effect.

Hydralazine + β blocker + diuretic

PK – 1st pass effect

Metabolism by acetylation

A/E

- **Reflex tachycardia, palpitations – May precipitate angina**
- **$Na+H_2O$ retention**
- **Drug induced lupus erythematous like Syndrome-slow acetylators**
- **Tolerance to effect**

Safe in pregnancy

Can be used in patients of HT with RF.

Inexpensive

Use restricted d/t side effects

25 mg day – 100 mg/day

Minoxidil

- **Arteriolar dilator-opening of potassium channels in smooth muscle-efflux of K^+**
- **Decrease in P.R**

S/E – Excess hair growth on face, back , arms. so not used

- **Treatment – Alopecia-2%solution-1ml twice a day**
- Enhanced microcirculation around hair follicles and also by direct stimulation of follicles
- Alteration of androgen effect of hair follicles

Diazoxide

Minoxidil, Diazoxide – K^+ channel opener

Arteriolar dilator

Only used in hypertensive crises

S/E –

Tachycardia

NA+H_2O retention

Hyperglycemia

Treatment – Insulinoma

Sodium nitroprusside

Short duration of action

Mechanism of action

Relaxation of vascular smooth muscle cells by generating nitric oxide

Arteriolar + venous dilatation

↓P.R. **↓Preload**

Balanced vasodilator

No reflex tachycardia

No Na + H_2O retention

PK

- **Onset 30 sec**
- **Duration 2.5 mins**
- **Given as I.V infusion**
- **Solution to be freshly prepared**
- **It decomposes on exposure to light – so infusion bottle to be covered with black paper.**

A/E

Hypotension

Dose- 50 mg in 500 ml of 5% Dextrose – 03-0.5 mcg / kg / min

Hypertensive emergency

ACE INHIBITORS

Renin- Angiotensin – Aldosterone system

Imp role – Regulation B.P.

Regulation of water electrolyte balance.

Renin – glycoprotein secreted by JG cells

Secretion regulated by

1) B_1® on JG cells

2) Change in tubular Na Con

3) Alteration in B.P.

fall in B.P.

↓

decrease renal perfusion

production of angiotensin

Angiotensinogen (Liver)

↓ **Renin**

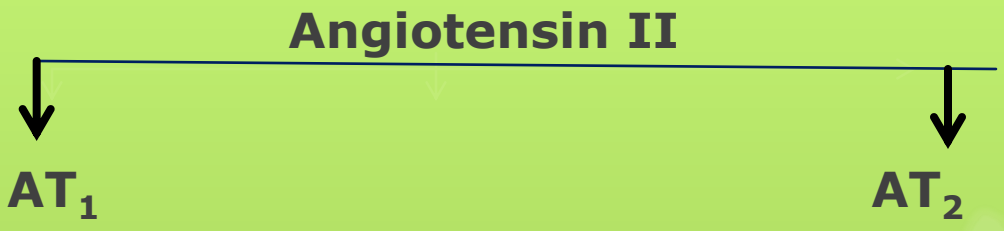
Angiotensin I

↓ **Angiotensin converting enzyme**

Angiotensin II

↓

Angiotensin III



Main mediator of effects of Angiotensin II

Actions of Angiotensin II

1) Peripheral vessels

Vasoconstriction of arterioles and veins

↑ **P.R.** ↑ **Venous return to heart**

a. **Angiotesin II acts on AT_1 receptors situated on VSM**

b. **facilitates peripheral noradrenergic neurotransmission by increasing**

   1) NE Release from sympathetic nerve terminal

   2) Inhibiting NE reuptake

c. **Increases central sympathetic outflow**

d. **Increases release of adrenaline from adrenal medulla.**

2) Causes aldosterone release from adrenal gland. Aldosterone causes Na+H_2O retention by acting at collecting tubule

3) Effects on heart

Angiotensin II locally produced in the heart.

1) **Cardiac hypertrophy, Hyperplasia**
2) **Increases migration, proliferation and hypertrophy of cells-Promoter of cell growth**

1) **↑ volume overload and P.R – Remodeling.**

4)Effect on GFR.

Normal person – Hardly any effect.

In a patient with bilateral renal artery stenosis

- **↑ angiotensin II Production**
- **It maintains GFR by constricting efferent arteriole**
- **ACE inhibitors CI –Renal failure may occur**

ACE INHIBITORS

Actions

1) Prevents conversion of angiotensin I to angiotensin II. So all effects of angiotensin II will not be there
2) ACE inactivates bradykinin. ACE inhibitor prevents breakdown of bradykinin. Bradykinin causes vasodilatation.

Uses

1. Hypertension

a. Prevents vasoconstriction by angiotensin II as there is decreased production of it .

b. Decrease availability of NE

c. Both these actions are responsible for in decrease in P.R.

d. Decrease production of aldosterone -less sodium water retention

e. Bradykinin metabolism inhibited - prolong vasodilatation

f. Renal vasodilatation – Natriuresis

g. Decrease formation of angiotensin II in myocardium – Prevents hypertrophy

Advantages over other antihypertensives

1. **No postural hypotension**
2. **Not CI in DM , BA**
3. **No change in H.R.**
4. **Can be used in CHF**
5. **Prevents cardiac hypertrophy**
6. **Prevents Diabetic nephropathy**
7. **No interference with baroreceptor reflex.**

2. Congestive cardiac failure.

a) Dilatation of arterioles – decrease P.R., decrease afterload on heart.

b) dilates veins - ⇓ venous return to heart

⇓

⇓ volume overload on heart

⇓

pulmonary edema.

c) Renal vasodilatation – Natriuresis

d) Decrease aldosterone release – Less Sodium water retention - edema

e) ⇓ NE release

f) Decrease sympathetic over activity which occurs in CCF.

3. Myocardial infarction

ACE inhibitors should be started as soon as possible

Decrease preload on heart

Decrease End diastolic volume

Decrease workload on ventricles

Stretch on ventricular wall reduced

Epicardial coronary vessels relieved

Hypertrophy of non- infarcted ventricular wall is prevented.

Protect against sudden death and second myocardial infarction after acute MI

Prevent heart failure after MI

4. Renal protection by ACE inhibitors

a. ↓ Synthesis of angiotensin II

↓

↓ renal efferent arteriolar constriction

↓

Prevents glomerular injury

b. ACE inhibitors enhance permeability selectivity of filtering membrane – so decrease micro-albuminuria. Decrease mesangial growth.

Both these actions are helpful in preventing diabetic nephropathy.

Captopril

Enalapril

Lisinopril

Ramipril

ACE inhibitors differ from each other in PK parameters.

Main route of elimination-Kidney

All are Prodrugs except captopril, lisinopril

Captopril

- 1st ACE inhibitor
- 1st dose effect

Dose – 6.25 mg- 25 mg TDS

Enalapril

a. It s a prodrug ,enalapril – enalaprilat
b. Absorption not affected by food
c. No 1st dose effect
d. Longer duration of action – OD or BD
e. No loss of taste
f. 5-10 mg BD

Lisinopril

10-20 mg OD

Cost

More

Adverse – effects

1. Cough – Dry, Brassy, Irritating non produtive
   - Exact reason not known
   - May be d/t accumulation of bradykinin in lungs.
   - May require discontinuation of drug
   - Subsides within 4-6 days.
   - More common in elderly, Females
2. Hypotension
   - Occurs with 1st dose
   - To prevent – start with smaller dose
3. Hyperkalemia
   - D/t aldosterone release inhibition
   - Never combine with K+ sparing diuretic
4. Skin rash
5. Alteration or loss of taste
6. ARF- In patients of bilateral renal artery stenosis
7. Angioneurotic edema
8. Tetratogenic

Angiotensin II Receptor Antagonist

Losartan – Blocks AT_1 receptors

No inhibition of metabolism of bradykinin

Decrease incidence of cough, Angioneurotic edema

Approach to a patient

B.P. – Every month

Lipid profile once a year

ECG every year.

Non-pharmacological Treatment **Pharmacological Treatment**

Diastolic B.P. 90 – 94

No other risk factor

2 Months trial before adding a drug

- **Smoking, alcohol – to be stopped**
- **Regular exercise**
- **Wt . Reduction**
- **Restrict Na^+ Intake ,** Potassium supplementation-3500–5000 mg/d
- **Stress relief measures**
- **Diet rich in fruits- vegetables, whole grains -**DASH dietary pattern
- **Low fat diet**

Goals of treatment

- BP target of less than 130/80 mm Hg is recommended.
- **Relieve symptoms**
- **Prevent complications – MI**
  Cerebral stroke
  HI encephalopathy
  Renal insufficiency
  Retinal hemorrhage

Diuretics	β Blockers	Clonidine methyldopa	Ca^{++} channel blockers	ACE inhibitors
Still remain 1st drug of choice cheap, S/E – less at low dose	Many CI Asthma DM Impair lipid Metabolism Cheap	Use limited d/t S/Es Methyldopa pregnancy	Can safely be used where β blockers are CI Expensive Quality of life good	Well tolerated. Quality of life- good. No S/E except cough

Pharmacological treatment

50 -70% patients respond to any one drug

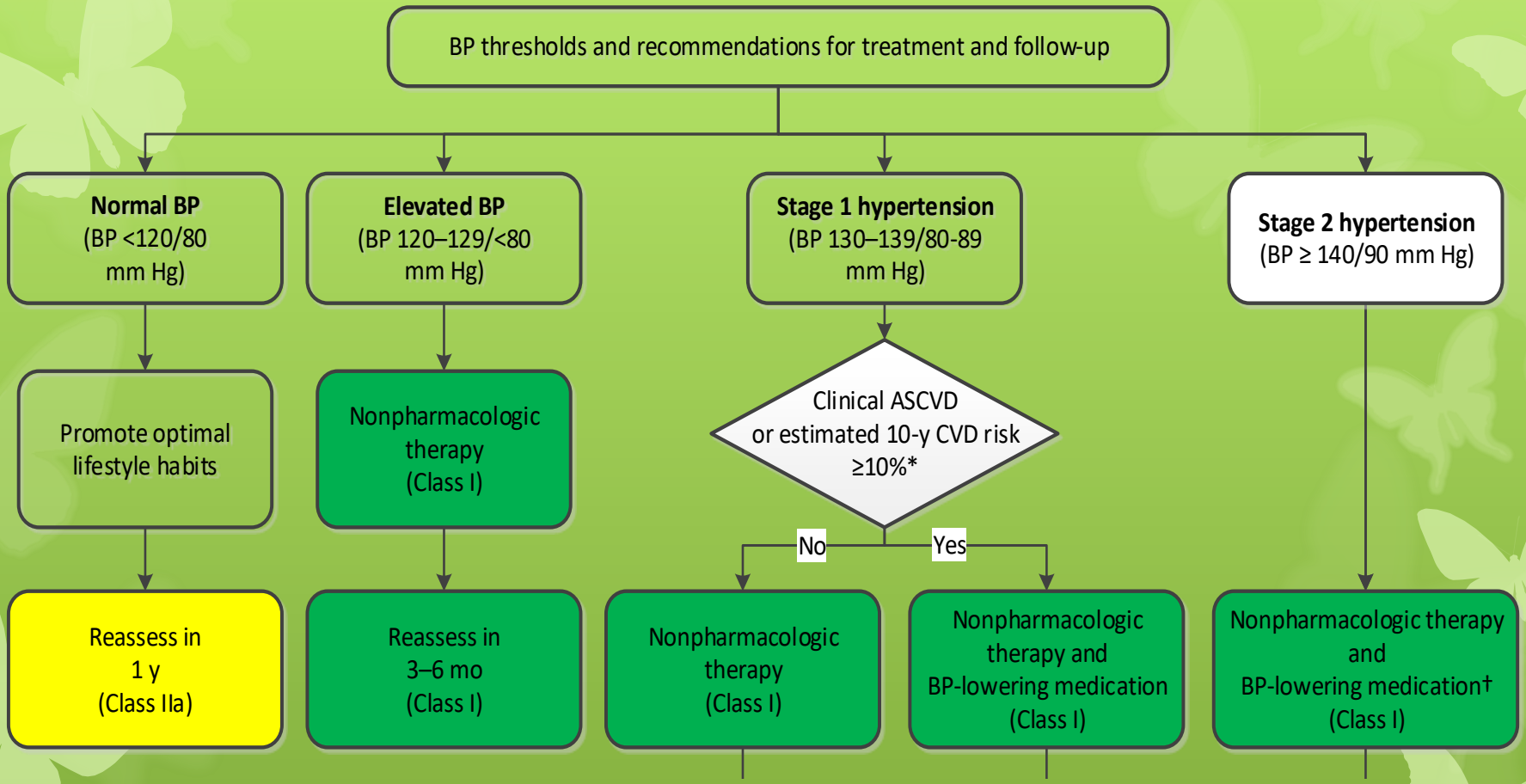
Individualized treatment- Tailored care approach

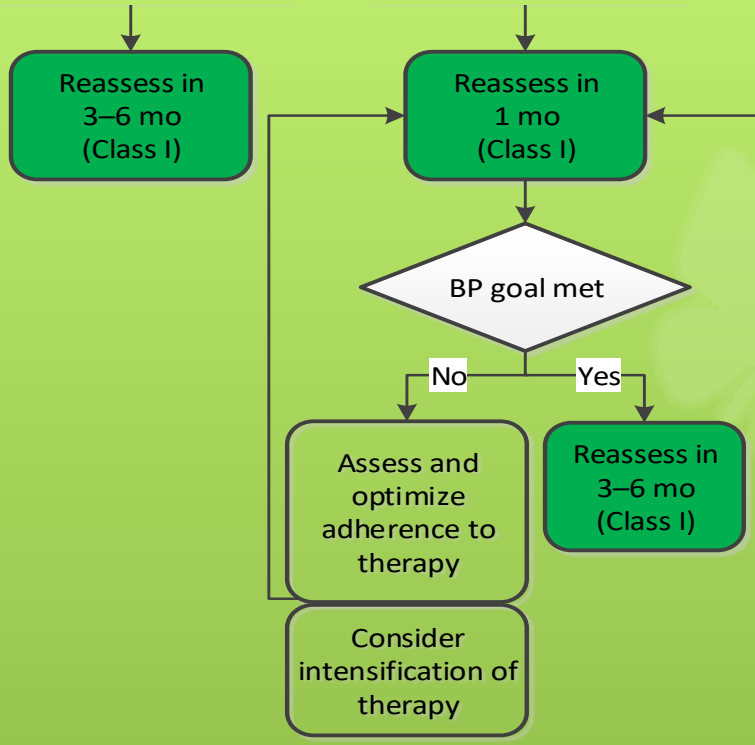
- **Tailoring choice of drug to the individual patient taking into the account total risk factors.**
- **According to patient's needs a drug is chosen –age, associated disease, drug's S/E**
- **Dose not to be increased till maximum tolerated dose**
- **An another drug is added**
- **Less S/Es Quality of life good**
- **Better compliance Cost less**

- For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

- Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg
- Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up (continued on next slide)





Colors correspond to Class of Recommendation in Table 1.

*Using the ACC/AHA Pooled Cohort Equations. Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy.

†Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP ≥160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.

Two drugs are combined together to treat HT

Advantages

1. **Additive / synergistic effect**
2. **counteracts S/Es of other drug**
3. **Decrease dose of individual drugs**
4. **decrease S/Es**
5. **Cost**

Atenolol + Amlodipine

Thiazides + β blockers

Thiazide + ACE inhibitor

Hydralazine + Thiazide + β blocker

Losartan + Thiazide

Guidelines for selecting 1st line drugs

- **HT- No other risk factor**

Thiazide, β blocker, Ca^{++} channel blocker ,ACE inhibitor

HT with angina

β Blocker

Ca^{++} channel blocker

- **HT + Hyperlipidemia**

  Don't give β blockers, thiazides as they raise LDL

  ACE inhibitors, Ca^{++} channel blockers

  No effect on lipid profile

  α blockers - ↓ LDL

- **Elderly HT . Pts**

  Clinical trials – Thiazides are better

- **Pregnancy**

1. **Methyl dopa**
2. **Hydralazine, Ca^{++} channel blockers, β_1 blocker, Labetalol**

HYPERTENSIVE CRISES

Sudden elevation of B.P.

1)Hypertensive emergency

Rapid, severe elevation of diastolic B.P. which leads to significant irreversible end- organ damage within hours if not treated, B.P. to be reduced within mins to 1 hr.

2) Hypertensive urgency

Elevation of B.P will not cause immediate end-organ damage, but to be reduced in 24 hrs.

Drastic reduction of B.P. to be avoided

Treatment – of hypertensive emergency

Parenteral route of drug administration

1-Nicardipine – better tolerated, less toxic - replacing nitroprusside

Esmolol or Labetalol to be coadministered

1. Sodium nitroprusside

Drug of choice

- **0.3 – 0.5 micrograms/ kg/min**
- **50 mg in 500 ml of 5% Dextrose**
- **It is preferred over nifedipine as dose can be adjusted according to B.P**
- **Continuous monitoring must**

2. Nitroglycerine

0.5 microgram/kg/min

less potent

3. Labetalol

4.Esmolol

4. Furosemide – 80 mg I.V.- To counteract volume overload

Other drugs that can be used

1) **Diazoxide**
2) **Hydralazine**
3) **Esmolol**

Hypertensive urgency

Usually parenteral drug administration not required

Hospitalize for 24 hrs

Treatment

Nifedipine – 10 mg S/L or gelatin capsule chewed swallowed

- Never exceed 1st dose 10 mg

Other drugs that can be used

Clonidine

Captopril

After control of B.P start previous medication

Newer drugs

1. 5 HT Antagonist

Ketanserin

5 HT2A ® blocking property

α1 blocking property more imp

3. K+ Channel openers

Nicorandil

Chromokalin

MOA: Leaking of K+ due to opening – hyper polarization of SMCs – relaxation of SMCs

4. Celiprolol

β1 blocker with β2 agonistic activity

5.Carvedilol

α + β blocker

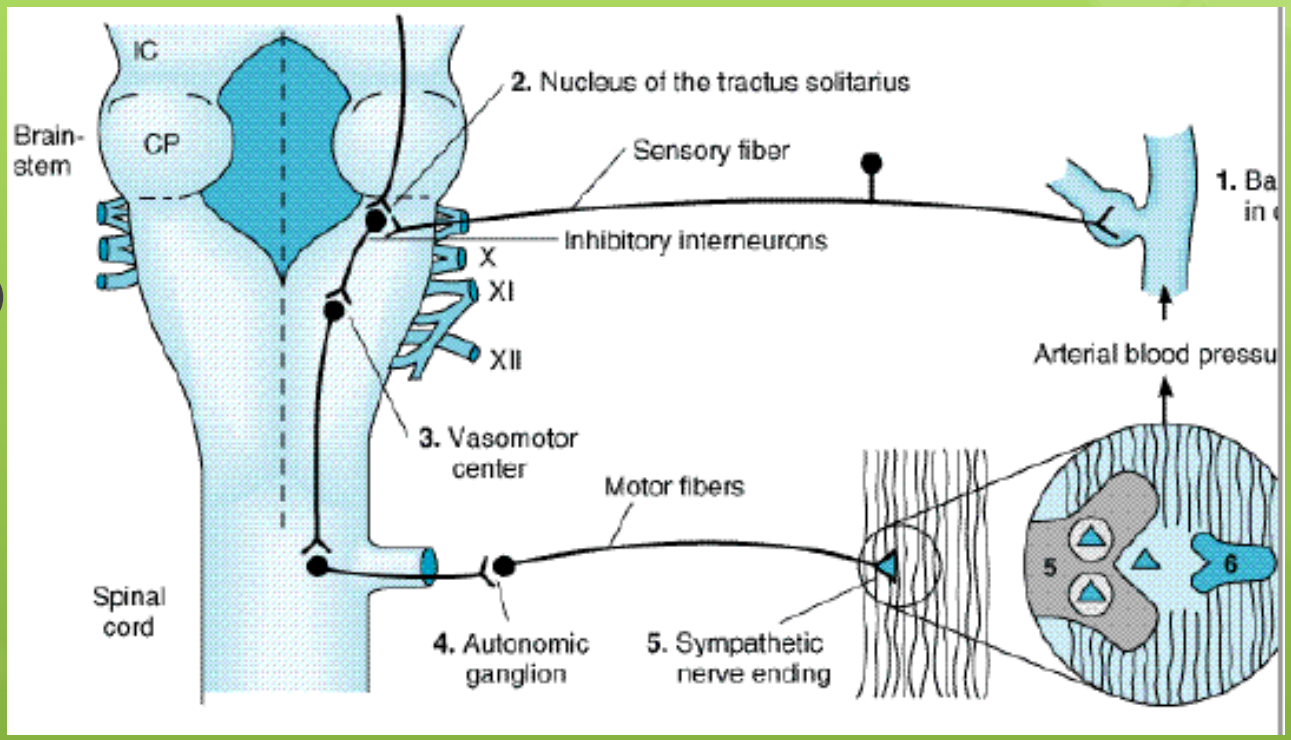
6.Renin antagonist

Aliskiren

Calcium Channel Blockers Examples

- Verapamil — Very
- Procardia (nifedipine)-HTN — Nice
- Cardizem (diltiazem)-arrythmias — Drugs

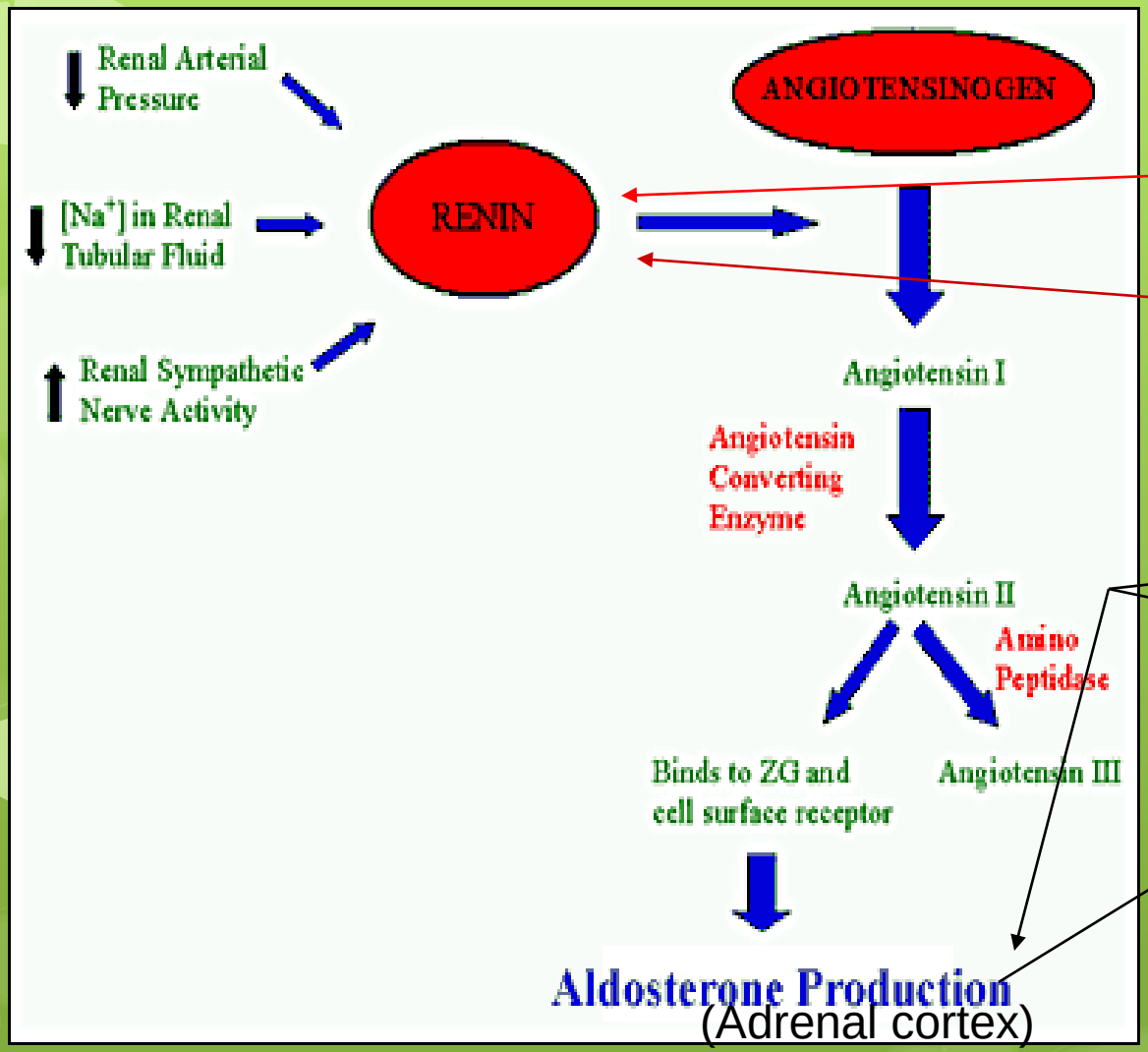
Baroreceptor reflex arc



If BP is high:
- ↓ CO and PR ⇨ ↓ BP

If BP is low:
- ↑ CO and PR ⇨ ↑ BP

RAS - Physiology



Increased Blood Vol.

Rise in BP

Vasoconstriction

Na+ & water retention

Kidney

Normal Blood Pressure Regulation

Blood Pressure = Cardiac output (CO) X Resistance to passage of blood through precapillary arterioles (PVR)

- Physiologically CO and PVR is maintained minute to minute by – arterioles (1) postcapillary venules (2) and Heart (3)
- Kidney is the fourth site – volume of intravascular fluid
- Baroreflex, humoral mechanism and renin-angiotensin-aldosterone system regulates the above 4 sites
- Local agents like Nitric oxide
- In hypertensives – Baroreflex and renal blood-volume control system – set at higher level
- All antihypertensives act via interfering with normal mechanisms