Antihypertensive-II

DR. JAYANT PATHARKAR
ASSISTANT PROFESSOR,
DEPT OF PHARMACOLOGY
SMT. B.K. SHAH MEDICAL INSTITUTE & RESEARCH CENTRE,
SUMANDEEP VIDYAPEETH DEEMED TO BE UNIVERSITY,
PIPARIA

β- Adrenergic blocking agent

- The exact mechanism of antihypertensive action of β-adrenergic blocking agent not clear
- But antihypertensive action can be correlated to their β1 adrenergic blocking action
- Peripheral vascular resistance is reduced during chronic administration
- Lipid soluble drugs like propranolol have central effect by reducing central outflow.

Pharmacological actions:

- They moderately lower SBP & DBP both in supine & standing position
- Prevent tachycardia caused by vasodilators
- Protect against stress induced hypertension
- They do not block baroreceptor mechanisms
- Hence, do not cause postural hypotension

- They are cardioprotective , especially in patients with IHD
- They do not impair kidney function
- They are generally safe & cost effective

Adverse reactions:

- These drugs are well tolerated & cause minimal adverse effects
- Bradycardia is common
- Tachycardia, rebound rise in blood pressure, angina pectoris: If β blockers are stopped abruptly
- As β receptors density increases on chronic administration

- Cardiac enlargement is relative contraindication
- NSAIDs reduce antihypertensive effect of β blockers
- As NSAIDs cause Na+ retention because of inhibition of renal prostacyclin (PGI2)
- CNS adverse effects: Highly lipid soluble drugs like propranolol, metoprolol can cause CNS adverse effects

- Therapeutic uses: β blockers are used to treat all grades of hypertension
- Relatively selective β1 blockers are preferred
- i.e. Atenolol

III. α & β adrenergic blocking agents:

- They act by competitively blocking both α1 & β receptor
- Thus, they reduce the BP in hypertensive patients
- i.e. Labetalol Dose : 100 mg twice daily can be increased gradually to 400-800 mg
- Carvedilol 6.25 mg twice daily used in CHF

Hypertension Therapy

- It is very much essential to treat hypertension as it causes cardiovascular diseases
- It also causes end-organ damage leading to mortality like kidney, eye, heart
- Reduction of BP can prevents renal, cardiac & cerebral complications

Pretreatment evaluation of cardiovascular diseases

1. Multiple BP reading in supine & standing position

2. Assessment of target organ damage:

a. Detailed history & physical examination
Dyspnoea, polyuria, nocturia, oedema, cardiomegaly

b. Urine examination, serum creatinine, serum electrolyte

c. ECG, X-ray chest, 2D-Echo

d. Fundoscopy: Condition of retinal blood vessels

3. Assessment for other cardiovascular risk factors:

Salt intake, alcohol consumption, smoking, obesity, diabetes, hyperlipidaemia

4. Special investigations to identify the cause of hypertension

These are done if hypertension is drug resistant

USG of renal blood vessels, renal angiography,

Tests for pheochromocytoma, aldosteronoma

Cardiovascular risk factors

1. Age > 55 years (men), > 65 years (women)
2. Family h/o premature CV disease
3. Smoking
4. Dysiipidemia (↑LDL, ↓HDL, ↑TG)
5. Diabetes mellitus
6. Hypertension
7. Obesity (BMI ≥ 30)
8. CKD (Microalbuminuria or g.f.r. < 60 ml/min)
9. Sedentary life style

Classification of Hypertension

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	< 120	< 80
High normal (Prehypertension)	120-139	80-89
Hypertension		
Mild	140-159	90-99
Moderate	160-179	100-109
Severe	180-209	110-119
Very severe	> Or = 210	> Or = 120

Grading of Hypertension:

BP		
Hypertension	*Systolic*	*Diastolic*
Stage I	140–159	90–99
Stage II	160–179	100–109
Severe	≥ 180	≥ 110

Compelling indications for specific antihypertensive drug classes

Diuretics	
1.	Heart failure
2.	High coronary artery disease risk
3.	Recurrent stroke prevention
ACE inhibitors/ARBs	
1.	Heart failure
2.	Post-myocardial infarction
3.	High coronary artery disease risk
4.	Diabetes
5.	Chronic kidney disease
6.	Recurrent stroke prevention
Calcium channel blockers	
1.	Diabetes
2.	Stroke prevention
β-Adrenergic blockers	
1.	Stable heart failure
2.	Post-myocardial infarction
3.	High coronary artery disease risk

Principles of Drug therapy

- In the past, evaluation of thiazide diuretics, Beta blockers, ACE inhibitors/ARBs and CCBs in large randomized trials with morbidity and mortality end points, established these drugs as first line antihypertensive drugs.

- However, the latest hypertension treatment guidelines (J C 8. NICE 201 1) have excluded Beta blockers from the list of first line drugs due to their lower efficacy in primary prevention of MI and stroke as well as other drawbacks

Principles of Drug therapy

- It is required to keep BP near normal
- SBP < 140 mm Hg & DBP < 90 mm Hg
- However, for patients aged >60 years the JNC 8 (2014) has suggested threshold systolic BP value of 150 mm Hg for initiating treatment, as well as to be the treatment goal (< 150 mm Hg). The threshold and goal diastolic BP value of 90 mm Hg is the same as for patients < 60 years of age
- Antihypertensive drugs are started in low dose & increased gradually
- i.e. start low & go slow

- Drugs like thiazides, ACEIs, ARBs & CCBs do not cause significant postural hypotension
- In patients with severe hypertension & very severe hypertension DBP should be lowered to 100-110 mm Hg in first 24 hr
- Further lowering is carried out in next 2-3 days
- Rebound hypertension if abrupt stoppage of antihypertensive drugs like β-blockers

Choice of drug therapy:

- Drug therapy of hypertension should be tailor made (patient guided)
- Drugs like thiazide-like diuretics, ACEIs, ARBs, CCBs can be used for initial therapy of hypertension
- Generally, thiazides/CCBs are preferred for elderly > 60 years of age

- RAAS inhibitors like ACEIs or ARBs can be used in younger patients
- ACEIs or ARBs are first choice drugs in CKD patients
- ACEIs in patients with LV dysfunction or DM
- Beta blockers/ CCBs in patients with stable angina pectoris

Use of drug combinations:

- Combination of antihypertensive drugs
- Advantages:
- Achieve better control of BP
- Reduce incidence of ADR as dose of individual drug is reduced

- Fixed dose combination ensure better patients compliance
- Rational combinations – antihypertensive drugs with different pharmacodynamic actions or with different anatomical site of action
- i.e. diuretics can be combined with vasodilator, methyldopa or ACEIs
- Possible hypokalaemia following thiazides can be countered by ACEIs

Management of Hypertension with drugs:

- Generally **stepped-care approach** is recommended

1. Start with low dose & monotherapy according to patients comorbid condition like DM, angina, pregnancy

2. If BP is not controlled another drug from different class is added

3. When two agents are used one of them should be diuretic i.e. low dose thiazide

4. Low dose combination therapy include

Thiazide with

a. Long acting CCB (amlodipine) or

b. ACEI or

c. ARB

- A CCB can be combined with ACEI/ ARB

- Two drug combination will control BP in 90% of patients

- If it is still not control than dose of primary agent increased to the full dose
- i.e. enalapril 20 mg, atenolol 50 mg or diltiazem 360 mg

5. Third drug added if BP is still not controlled

6. If BP is still not controlled than patients should be fully investigated for possible cause of ***secondary hypertension***

Step 1

- ***Young (< 55 years) non-black subjects*** generally have higher plasma renin activity, they respond better to ***ACE inhibitors/ ARBs***, while older patients and blacks of any age have lower renin status and show a weaker response to ACE inhibitors/ARBs.
- Accordingly, JNC8 recommend initiating antihypertensive therapy with any one of thiazide diuretic, or ACE inhibitor/ARBs or CCB for young (< 55 years) non-blacks,
- but the options for blacks of any age and older non-blacks are either thiazide or CCB

Step 2

- When the target BP is not attained by a single drug a combination of two drugs, i.e. ***ACE inhibitor/ARB*** + ***CCB or diuretic*** if CCB not suitable, is recommended irrespective of the age or race of the patient.
- In selected cases where therapy has been initiated with a Beta blocker, the second drug should be a CCB. Combination of Beta blocker with diuretic is to be avoided, because this increases the risk of developing diabetes.
- Initiating antihypertensive therapy with two drugs is advised by JNC8 in case the BP at diagnosis is >20 mm Hg systolic and/or > 10 mm Hg diastolic higher than the goal BP.

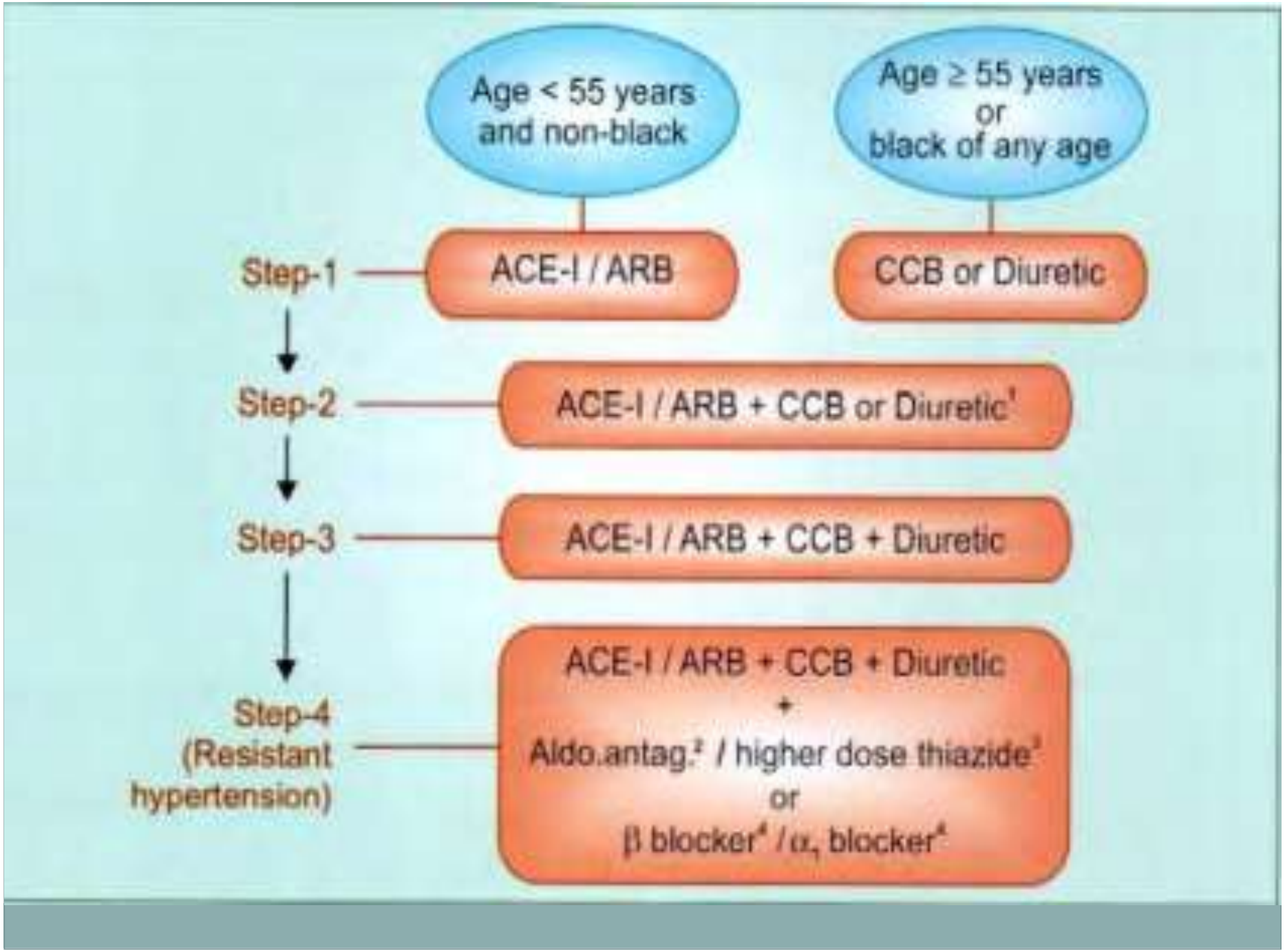
Step 3

- The step 3 treatment includes all 3 first line drug classes, viz. ***ACE inhibitor/ARB + CCB + diuretic***.

- However, before adding the third drug, the dose of existing medication should be titrated to the optimal or the best tolerated.

Step 4

- Patients who do not achieve target BP even when taking optimal doses of 3 drugs are regarded as having resistant hypertension.
- Many patients having diabetes and/or CKD fall in this category.
- In such cases the NICE recommend adding a fourth drug, which can either be an ***aldosterone antagonist*** (if serum K is 4.5 mmol/L) or a ***Beta blocker*** (especially Beta blocker with vasodilating property, viz. carvedilol, nebivolol) or a selective alpha1 blocker.


Age < 55 years and non-black
Age ≥ 55 years or black of any age
Step-1
ACE-I / ARB
CCB or Diuretic
Step-2
ACE-I / ARB + CCB or Diuretic[1]
Step-3
ACE-I / ARB + CCB + Diuretic
Step-4 (Resistant hypertension)
ACE-I / ARB + CCB + Diuretic
+
Aldo.antag.[2] / higher dose thiazide[3]
or
β blocker[4] / α1 blocker[4]

Hypertension in elderly

- Increased diastolic BP & isolated SBP are cardiovascular risk factors in elderly patients
- Treatment of hypertension required when BP exceeds 150/90 mm Hg
- Rapid lowering of BP should not be tried
- Drug used are low dose thiazide/CCB
- ACEIs & ARBs can also be used
- Beta-blockers are not so useful but can be used in secondary prevention of MI or heart failure.

Hypertension in pregnancy:

- Hypertension in pregnant women:
- SBP > 135 mm Hg DBP > 85 mm Hg

- Hypertension in pregnancy needs to be treated to prevent pre-eclampsia

- Drug used:
- Methyldopa – safe for mother as well as baby

- It is preferred drug in pregnancy

- Alternatively Beta-blockers can be used in third trimester

- Other drugs used are Labetalol, extended release nifedipine

- ACEIs & ARBs are absolute contraindications in pregnancy

- Severe hypertension near term or during labour needs to be treated urgently
- In such cases **i.v. labetalol** is treatment of choice
- **Magnesium sulphate intravenously** – it is drug of choice for treatment & prevention of eclampsia convulsions
- Sodium nitroprusside is used only when other agents fails

Treatment of hypertensive crises:

- **Hypertensive urgency:** Sudden or severe elevation of BP DBP > 120 mm Hg or higher
- It has impending complications
- **Hypertensive emergencies :** severe elevation of BP to 210/120 -130 mm Hg with evidence of **target organ damage** or dysfunction
- Hypertensive crises should be treated in hospital ICU with the facilities for invasive BP monitoring

- Drugs which do not cause reduction in the perfusion of vital organs are used
- i.e. CCB, fenoldopam & sodium nitroprusside

- Drastic lowering of BP in few minutes should be avoided

- Otherwise it will cause cerebral ischemia, severe brain damage, may precipitate MI, Blindness & stroke

- Arteriolar & venous dilator:
- **Sodium nitroprusside:** 0.25 mcg/kg/min i.v. infusion

- **Nitroglycerine:** 5-100 mcg/min i.v. Infusion

- Arteriolar dilator:
- **Hydralazine :** 5-10 mg i.v. bolus every 30 min

- D1 receptor agonists
- **Fenoldopam :** 0.1-0.6 mcg/kg/min i.v. infusion

MCQs

Q 1. What are advantages of combinations of antihypertensive drugs

A) Achieve better control of BP

B)Reduce incidence of ADR

C) Improve patients compliance

D) All of the above

Q 2. Which are first line drugs to treat hypertension

A) Thiazides

B) ACEIs

C) CCBs

D) All of the above

Q 3. These drugs are used to treat moderate hypertension except

A) Alpha methyldopa

B) CCBs

C) ACEIs

D) None of the above

Q 4. These drugs are used for hypertension during pregnancy except

A) Alpha methyldopa

B) Labetalol

C) Magnesium sulphate

D) ACEIs

Q 5. These drugs are used in hypertensive crisis

A) Sodium nitroprusside

B) Nitroglycerine

C) Hydralazine

D) All of the above

Sr. No	Author	Topic	Journal /Book	Level
1	K D Tripathi	Antihypertensive drugs	Essentials of Medical Pharmacology, 8th edition	1
2	R S Satoskar	Pharmacotherapy of Hypertension, Pulmonary hypertension & Orthostatic hypotension	Pharmacology & Pharmacotherapeutics 25th Edition	1
3	Eduardo Hernandez-Vila, MD	A Review of the JNC 8 Blood Pressure Guideline	Texas Heart Institute Journal	3