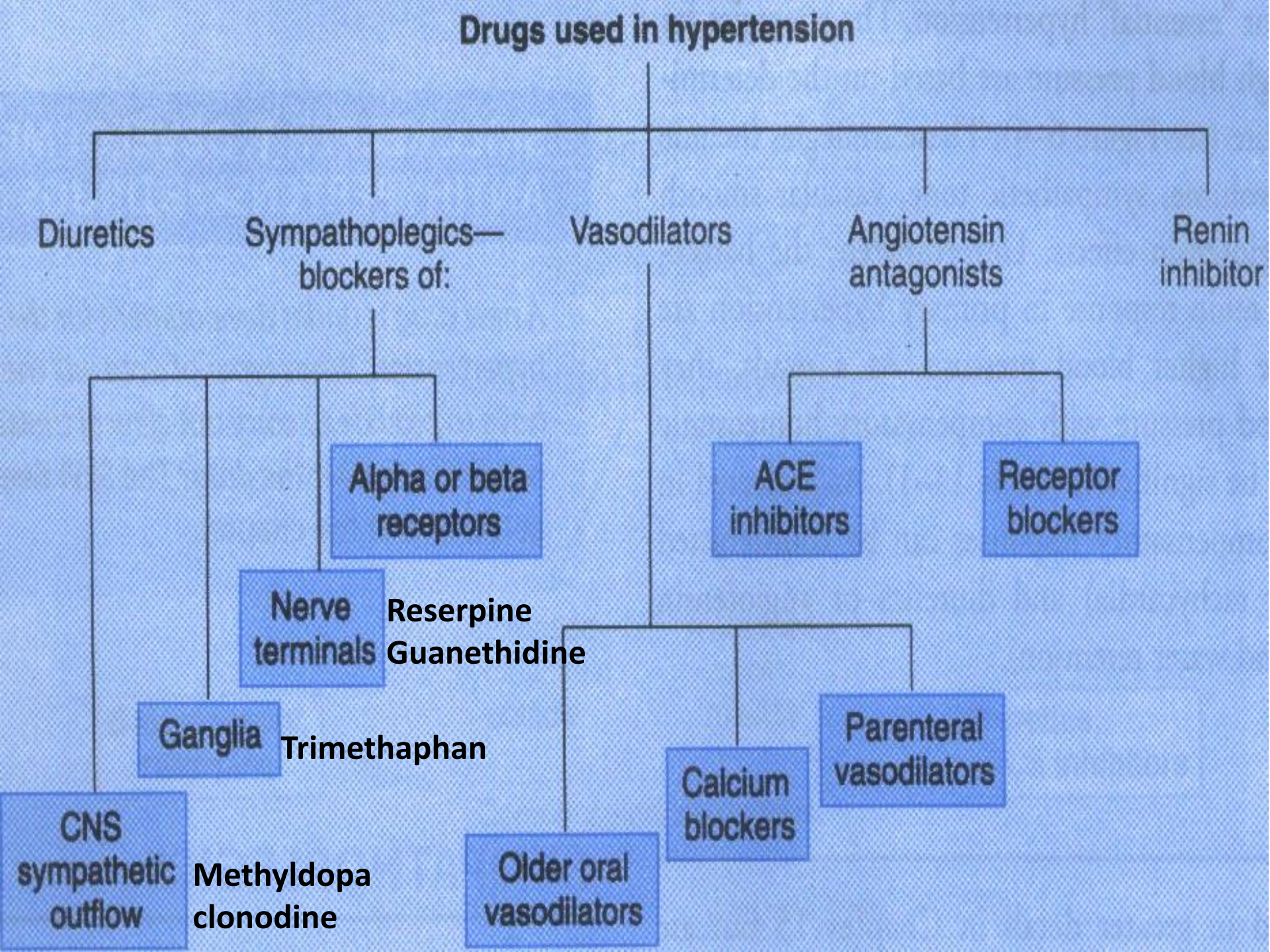
Drugs used in hypertension


Drugs used in hypertension
Diuretics
Sympathoplegics—blockers of:
Vasodilators
Angiotensin antagonists
Renin inhibitor
Alpha or beta receptors
Nerve terminals
Reserpine
Guanethidine
Ganglia
Trimethaphan
CNS sympathetic outflow
Methyldopa
clonodine
ACE inhibitors
Receptor blockers
Older oral vasodilators
Calcium blockers
Parenteral vasodilators

Centrally acting α 2 agonist

- **Diminish adrenergic out flow**
  - Reduced total peripheral resistance and a decreased BP
- **Clonidine**
  - Used for treatment of mild to moderate hypertension
  - Does not decrease renal blood flow or GFR
  - Useful in hypertension with renal disease
  - Causes Na+ and water retention. Used with diuretic
  - Sedation and dryness of nasal mucosa
  - **Rebound hypertension** occurs following abrupt withdrawal
- **α Methyldopa**

Methyldopa

- **Hypertension in pregnancy**
- Taken up by noradrenergic neurons --- Converted to α methylnorepinephrine --- **false neurotransmitter**
- Centrally acting α_2 agonist
- Diminish adrenergic out flow
  - Reduced total peripheral resistance and a decreased BP
- Adverse effects
  - Sedation and drowsiness
  - Immune hemolytic reactions
  - Liver toxicity

Vasodilators

- Vasodilators act
  - To increase local tissue blood flow
  - To reduce arterial pressure
  - To reduce central venous pressure
- Net effect is reduction of cardiac work by a reduction of cardiac
  - **Preload** (reduced filling pressure) and
  - **Afterload** (reduced vascular resistance)

Main uses of vasodilators

- **Antihypertensive** therapy
  - ACE I, AT_1 antagonists (ARB), CCB and α_1 antagonists
- Treatment and prophylaxis of **angina pectoris**
  - CCB, Nitrates
- Treatment of **cardiac failure**
  - ACE I, ARB

Vasodilators

- Arteriolar dilators (↓ after-load)
  - **Hydralazine, Minoxidil, Ca^{++} channel blockers**
  - Fenoldopam (dopamine D1 receptor activator)
- Venodilators (↓ pre-load)
  - **Nitrates**
- Mixed dilators(↓ pre and after load)
  - **ACE inhibitors, ARB**
  - **Prazosin (α 1 blocker)**
  - **Nitroprusside**

Indirectly acting vasodilator dugs

- The **renin-angiotensin-aldosterone system** can be inhibited at several points
  - **Renin release** ---- β blockers
  - **Renin activity** – renin inhibitors (aliskiren)
  - **ACE I**
  - **ARBs** ---- receptor AT_1 inhibitors
  - Aldosterone receptor antagonists
- All such drugs can increase plasma K+ concentration by reducing aldosterone secretion or action

Calcium channel blockers (CCBs)

- These drugs block **voltage gated L-type (slow)** Ca^{++} channels in **cardiac and smooth muscles**
  - Prevent opening of the channels --- Ca^{++} influx is ↓ed during A P --- reduced intracellular Ca^{++} concentration and muscle contractility
- **Ca^{++} channels used in neurotransmission (N-,P-, and R-types) or hormone release [secretory cells] use L types which are different and not blocked by CCB**

Ca^{++} channel blockers

- **Non-dihydropyridines**
  - Diphenylalkylamines **Verapamil**
  - Benzothiazepines **Diltiazem**
- **Dihydropyridines**
  - First generation **Nifedipine**
  - 2^{nd} generation
  - **Amlodipine**, Felodipine, Isradipine, **Nicardipine**,
  - Greater affinity for vascular Ca^{++} channels than for Ca^{++} channels in the heart
  - Little interaction with digoxin or warfarin

Effects --- CCB

- **Relax smooth muscles of arteries**, but they **do not much affect the veins**
  - To a lesser extent relax other smooth muscles (uterus, bronchi, gut, biliary tract, urinary tract) are less important therapeutically --- adverse effects
- **Block Ca^{++} dependent conduction in A-V node** (verapamil and diltiazem)
  - The heart rate and contractility are reduced

CCB and BV

- Affect all vascular beds, although regional effects vary between different drugs
- **Coronary vasodilatation** and relief of spasm Used in coronary artery spasm (variant angina)
- **Dilate arterioles** and ↓ after load --- hypertension

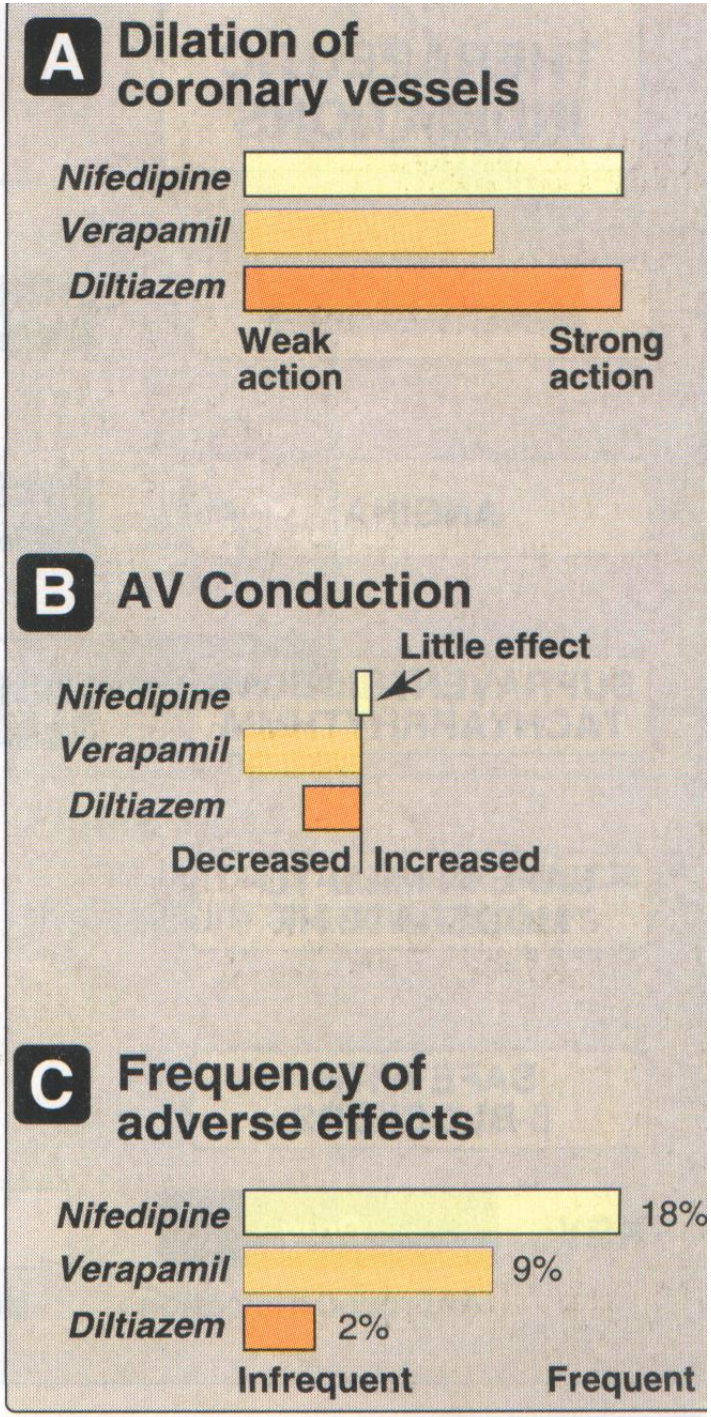
Selectivity between heart / smooth muscle of BV

- **Verapamil** is relatively cardioselective
- **Nifedipine** is relatively smooth muscle selective, and **diltiazem** is intermediate
- **Vasodilator effect (mainly dihydropyridines)** is mainly on resistance vessels, reducing after load
- **Nifedipine** and other DHPs (dihydropyridines) evoke great vasodilatation --- **Reflex tachycardia**

Effects --- CCB

- All reduce BP
- Reduce double product
  - A measure of cardiac work and O2 requirement
  - Systolic BP x heart rate

	Verapamil	Nifedipine	Diltiazem
Heart Rate	↓	↑	↓, –
A-V conduction velocity	↓↓	–	↓
Contractility	–, ↓	↑	↓, ↑
Output	–, ↓	↑	–, ↑
BV smooth muscle relaxation	++	+++	+
Clinical uses	Angina, arrhythmia, (HTN)	Angina, HTN	Angina, HTN, (arrhythmia)


A
Dilation of coronary vessels
Nifedipine
Verapamil
Diltiazem
Weak action
Strong action
B
AV Conduction
Little effect
Nifedipine
Verapamil
Diltiazem
Decreased
Increased
C
Frequency of adverse effects
Nifedipine
18%
Verapamil
9%
Diltiazem
2%
Infrequent
Frequent

Therapeutic uses

Angina pectoris

- **Coronary vasodilatation** and relief of spasm Used in coronary artery spasm (variant angina)

Hypertension

- **Dilate arterioles** and ↓ after load

Class IV antiarrhythmic drugs

(verapamil, diltiazem**)**

Therapeutic uses – effect on vascular smooth muscles

- **Angina pectoris --- e.g., diltiazem, DHPs**
  - As prophylactic therapy in both effort and vasospastic (variant)angina
  - Particularly useful **with nitrates** in severe atheroscrerotic angina
- **Hypertension**
  - Asthma, DM, angina, and/or peripheral vascular disease
  - **mainly dihydropyridines (e.g., amlodipine or slow release nifedipine)**

Therapeutic uses – effect on A-V node

- **Block Ca^{++} dependent conduction in A-V node** (verapamil and diltiazem)
- **Class IV antiarrhythmic drugs -- Verapamil**, diltiazem
  - **S V T**achyarrhyrthmia
  - To slow ventricular rate in **rapid AF**
  - To prevent recurrence of SVT
  - I/V verapamil **to terminate an attack of SVT** has been replaced by **adenosine**

Other uses Ca++ channel blockers

- **Hypertrophic cardiomyopathy**
- **Hemorrhagic stroke**
  - **Nimodipine** (dihyropyramidine) has some selectivity for cerebral vaculature and is used to reduce vasospasm following subarachnoid hemorrhage
- Nifedipine in premature labor
- Verapamil in **nocturnal leg cramps**
- DHP's reduce severity of **Raynaud's phenomenon**
- **Migraine prophylaxis**
  - **Flunarizineis** relatively weak Ca^{++} channel blocker and also inhibit Na^{+} channel
  - Claimed to be as effective as propranolol

Pharmacokinetics --- CCBs

- Nifedipine, Diltiazem, and Verapamil have shorter half lives (3-8 hours)
  - to be given 3 times a day
  - Sustained release preparations has less frequent dosing
- Amlodipin has a long half life
  - It is given once daily
- CCBs well absorbed from GIT and are given orally
- I/V verapamil
  - PSVT

Adverse effects
Extension of pharmacological actions

- Headache and flushing --- vasodilator action
- **Ankle swelling** on chronic use
  - Arteriolar dilatation and ↑ permeability of postcapillary venules
- **Constipation --- verapamil**
  - Effect of Ca^{++} channels in the GIT smooth muscles
- Dizziness, headache
- Feeling of fatigue caused by a decrease in BP
- **CCB are free from idiosyncratic adverse effects**

Adverse effects --- heart

- Heart rate
  - **Verapamil** --- slows the heart --- heart block
  - **Diltiazem** causes little or no change in heart rate
  - **Nifedipine** typically causes **reflex tachycardia**
- Negative inotropic effect --- most CCBs --- may worsen heart failure
  - **Verapamil** has marked effect – contraindicated if heart failure
  - **Amlodipine** does not worsen cardiovascular mortality in patient with severe chronic heart failure

Verapamil

- **Angina pectoris, HTN, arrhythmia**
- **Highly negative ionotrpic and chronotropic**
  - Reduces cardiac output
  - Slows the heart rate
  - impair A-V conduction
- It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension in high doses
- **Should not be used with beta blockers**
- **Constipation**

Adverse effects

- Verapamil
  - Constipation (10%) and bradycardia are more common
  - Flushing, headache, and ankle edema are less common
- Hypotension is occasional and tachycardia (common with DHPs) is absent
- Contraindicated in 2nd, and 3rd degree heart block
- Precipitate CHF in patients with preexisting disease
- Verapamil to be avoided in CHF due to its –Ve ionotropic effects
- Dizziness, headache
- Feeling of fatigue caused by a decrease in BP

Adverse effects -- interaction

- Should not be given with β blockers ---- additive sinus depression
- Increases plasma digoxin level by decreasing its excretion
- Should not be used with other cardiac depressants like quinidine, disopyramide

Diltiazem

- **Angina pectoris,** HTN (long acting preparations), arrhythmia
- It may be used in patients for whom beta blockers are contraindicated or ineffective
- Less negative ionotropic effect than verapamil
- To be used with caution in association with beta blockers because of risk of bradycardia

Drug interaction

- Contraindicated
  - Verapamil with β blockers
- Use with caution
  - Verapamil with diltiazem
- Dihydropyridines can be used with β blockers
- DHPs has little interaction with digoxin or warfarin

Nifedipine

- It has more influence on vessels and less on myocardium than does verapamil
- Unlike verapamil has **no antiarrhythic activity**
- It rarely precipitate heart failure as negative ionotropic effect is offset by a reduction in LV work
- Safely administered with beta blockers and digoxin
- Short acting formulation
  - Are not recommended for angina or long term management of HTN
    - Large variation in BP and reflex tachycardia
    - Higher mortality in post MI patients

Amlodipine, felodipine

- Used for the treatment of **angina or HTN**
- **No antiarrhythic activity**
- Resemble nifedipine except
- Do not reduce myocardial contractility and do not produce clinical deterioration in heart failure
- They have a longer duration of action and can be give once daily
- They are valuable in angina associated with coronary vasospasm
- Side effects associated with vasodilatation such as **flushing and headache and ankle edema** are common

Nimodipine

- It is related to nifedipine but the smooth muscle relaxant effect preferently acts on cerebral arteries
- Use confined to prevention of vascular spasm following **aneurysmal subarachnoid hemorrhage**

Vasodilators

- Arteriolar dilators (↓ after-load)
  - **Hydralazine**
  - **Minoxidil**
  - **Ca^{++} channel blockers**
- Venodilators (↓ pre-load)
  - **Nitrates**
- Mixed dilators(↓ pre and after load)
  - **ACE inhibitors, ARB, prazosin (α 1 blocker)**
  - **Nitropruside**

Hydralazine --- direct vasodilatation

- Release of nitric oxide from drug or endothelium
- Arteries and arterioles -- ↓ peripheral resistance --- reflex tachycardia and cardiac out put
- ↑ myocardial contractility, heart rate, and **O2 consumption**
  - Precipitate angina pectoris, MI, or cardiac failure in predisposed individuals
  - Vasodilators also ↑ plasma renin concentration, resulting in sodium and water retention
- Almost always used in combination with a **beta blocker** (to balance reflex tachycardia) and a **diuretic** (to decrease sodium retention)

Hydralazine --- direct vasodilatation

- Used for short term treatment of **severe hypertension in pregnancy**

- Adverse effects
  - Headache, N ,sweating, arrhythmia, and precipitation of angina
  - SLE ---- A reversible lupus like syndrome

Minoxidil

- **Minixodil** and **Cromakalim** relax smooth muscle by selectively increasing the membrane permeability to K^+ by K_{ATP} channel activation
  - This hyperpolarizes the membrane and switches off voltage dependent Ca++ channels
- Dilatation of arterioles
- Do not affect capacitance vessels (venules)
- Reflex tachycardia may be severe
  - Require the concomitant use of beta blockers and diuretics
- Serious sodium and water retention
  - Volume overload , edema, and CHF
  - Hypertrichosis (the growth of body hair)
  - Used topically to treat male pattern baldness

Nitroprusside (Nitroferricyanide)

- A powerful vasodilator that **acts equally on arterial and venous smooth muscles**
- It reacts with tissue sulfhydryl groups to yield **NO**
- Used in intensive care units for **hypertensive emergencies** and to produce **controlled hypotension during surgery**
- Useful only for short term treatment (up to 72 hrs maximum)
- I/V infusion --- plasma half life being only a few minutes
- Must be freshly prepared from the dry powder and protected from light
- Rapidly converted to thiocyanate in the body
  - Prolong use thiocyanate accumulation and toxicity --- weakness, nausea, and inhibition of thyroid function

Combination therapy

- Most hypertensive patients will require a combination of antihypertensive drugs to achieve the recommended targets
- When monotherapy fails or is not tolerated Combine drugs with different mechanism of actions
  - Drugs which increase plasma renin activity with
    - Diuretics, vasodilators, CCBs, ACE I
  - drugs which lower plasma renin activity
    - Beta blockers, clonidine ,methyldopa

Useful combinations

- All sympathetic inhibitors (except β blockers) and vasodilators cause fluid retention. Addition of diuretic check fluid retention
- Vasodilators like Hydralazine and dihydropyridines (Nifedipine) cause tachycardia which is counteracted by beta blockers
- ACE I /AT1 antagonists are particularly synergistic with diuretics
  - Very good combination in patients with CHF and LVH
- ACE I + CCBs or betablockers or clonidine or methyldopa
- β blockers and prazosin

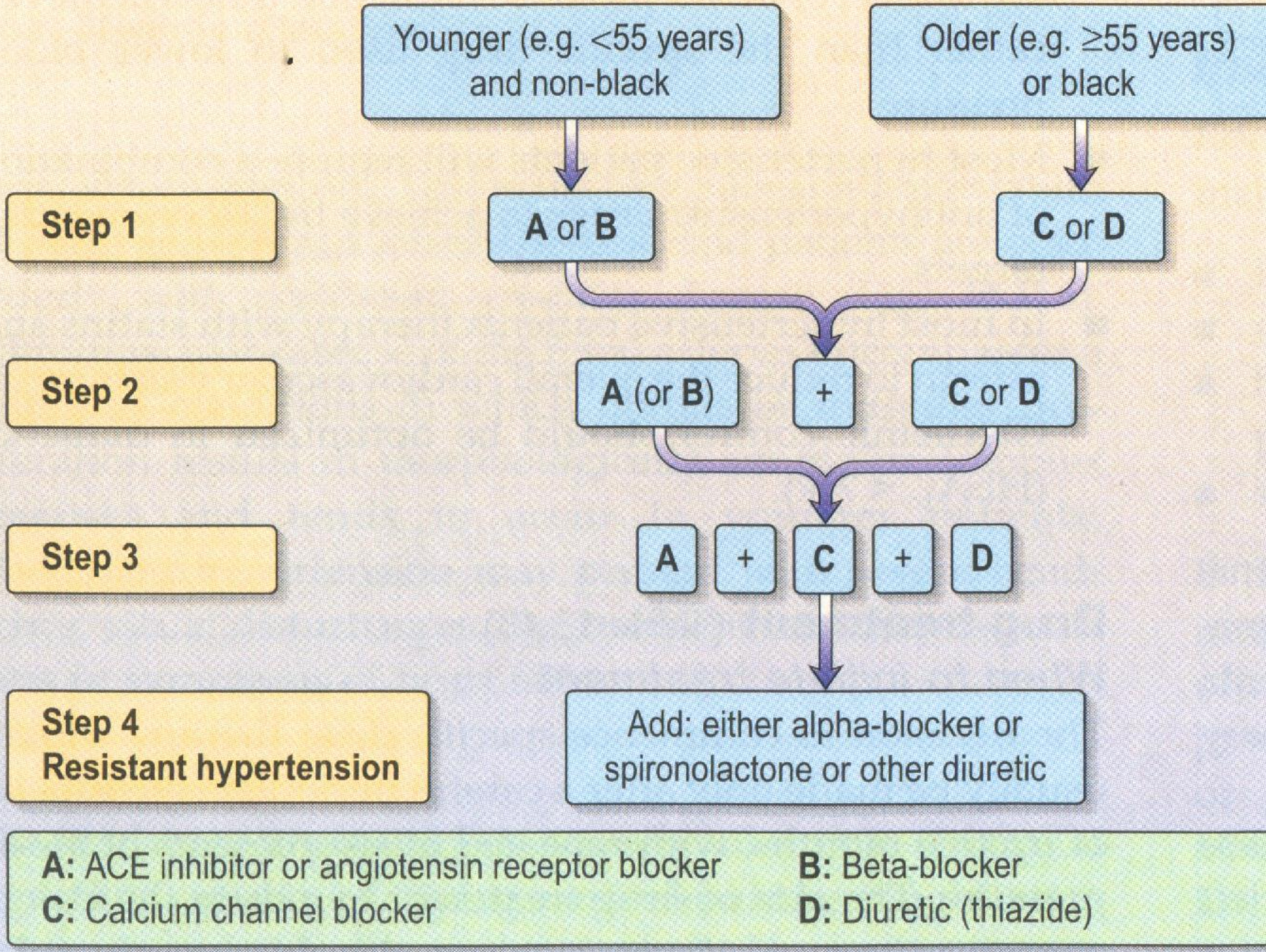
Combinations to be avoided

- Verapamil with beta blocker
  - Marked bradycardia , A-V block
- Any two drugs of the same class
  - Methyldopa with clonidine
  - Verapamil with dihydropyridines
- An α or β blocker with clonidine
- Nifedipine (or other dihydropyridines) with diuretics: synergism between these in not proven
- It is not advised to combine a diuretic with a beta blocker since both aggravate DM

Factors that influence the choice of the drugs

- Concomitant illness, age and subset of population
- Subset of Population --- **Black patients**
  - respond well to diuretics & CCBs
  - β blockers and ACE I are less effective
- **Elderly**
  - CCBs, ACE I and diuretic are favored
  - β blockers and α antagonists are less well tolerated
- β blockers
  - are more effective in white than in black and in young compared to elderly patients

The British Hypertensive Society recommendations


Younger (e.g. <55 years) and non-black
Older (e.g. ≥55 years) or black
Step 1
A or B
C or D
Step 2
A (or B)
+
C or D
Step 3
A
+
C
+
D
Step 4
Resistant hypertension
Add: either alpha-blocker or spironolactone or other diuretic
A: ACE inhibitor or angiotensin receptor blocker
B: Beta-blocker
C: Calcium channel blocker
D: Diuretic (thiazide)

HTN with concomitant disease

Angina pectoris	β blockers	CCBs			
Diabetes	ACE I	ARB	CCBs	Diuretics	β blockers
Recurrent stroke	ACEI		diuretics		
Heart failure	Diuretics	β blockers (low dose)	ACE	ARB	
Previous MI	β blockers	ACE I			
C RF	ACE	ARB	CCBs	β blockers	

Hypertension & pregnancy

- 8- 10 % of pregnancies
- When detected in first half of pregnancy or persisting after delivery is usually due to pre existing essential HTN
- HTN presenting in second half of Pregnancy------ or **pregnancy induced HTN ----** usually resolves after delivery

Hypertension during pregnancy

- **Preeclampsia**
  - After 20th weeks Pregnancy + HTN + proteinuria + generalized edema
- **Eclampsia**
  - Preeclampsia + generalized seizures
- **Chronic hypertension**
  - BP greater than 140/90 mmHg before the 20th week of pregnancy
- **Chronic HTN with superimposed preeclamsia or eclampsia**
- **Transient HTN**
  - Increase in BP without associated proteinuria or CNS manifestations
  - BP returns to normal within 10 days of delivery

Antihypertensives used in pregnancy

- Methyldopa
  - Mild HTN
  - Safe in pregnancy
- Labetalol (both α and β blocker)
- Pre-eclampsia
  - Methly dopa / labetalol
  - Nifedipine
- Moe severe HTN or eclampsia
  - I/V hydralazine
  - Termination of pregnancy

Antihypertensives to be avoided during pregnancy

- Diuretics
- ACE I / ARBs
- Reserpine
- Non selective beta blockers
- Sodium nitropruside contraindicated in eclampsia

Hypertensive emergency

- A life threatening situation
- In an otherwise healthy person
  - DBP > 150 mm Hg (with SBP > 210 mm Hg)
- In patients with pre-existing complications– encephalopathy, cerebral hemorrhage, LVF, aortic stenosis.
  - DBP > 130 mm Hg

Hypertensive emergencies

- **End organ damage determines the seriousness of emergency and approach to the patient**
- Emergencies include
  - Hypertensive encephalopathy
  - Hypertensive nephropathy
  - Intracranial haemorrhage
  - Aortic dissection
  - Preeclampsia-eclampsia
  - Pulmonary edema
  - Unstable angina
  - MI

Hypertensive emergency

- Accelerated or very severe hypertensive
  - Diastolic pressure > 140 mmHg
- Malignant HTN
  - Severe HTN + grade 3 or 4 retinopathy
- Hypertensive encephalopathy
- Severe hypertensive complications
  - Cardiac failure

Management of Hypertensive emergency

- Requires the reduction of BP to avoid the risk of morbidity and mortality
- Admission to hospital for immediate initiation of treatment
- Unwise to reduce the BP too rapidly
  - Can reduce organ perfusion leading to
  - Cerebral infarction and blindness,
  - Deterioration in renal function and
  - Myocardial ischemia

Management of Hypertensive emergency

- The initial goal of therapy is to reduce mean arterial BP by no more than 25% within minutes to 2 hours or to a BP in range of 160/100-110 mmHg
- Aim is
  - To reduce the diastolic BP to 100-110 mmHg over 24-48 hours
  - BP is then normalized over the next 2-3 days
- Normally treatment should be by mouth with a beta blocker or CCB
- Parenteral antihypertensive drugs are rarely necessary
- Nitropruside by infusion is the drug of choice

Parenteral agents in hypertensive emergency

- Nitroprusside sodium
- Nitroglycerine , I/v
- Labetalol (both α and β blocker)
- Esmolol
- Nicardipine I/V
- Fenoldopam
- Diazoxide – a thiazide derivative but lack diuretic properties
- Hydralazine
- Diuretics

Oral agents in hypertensive emergency

- Captopril S/L
  - 12.5 -25 mg orally will lower BP in 15-30 miutes
  - The response is variable and may be excessive
- Nifedipine S/L
  - **The effect is unpredictable and may be excessive, resulting in hypotension and reflex tachycardia**
  - **MI and stroke have been reported**
  - **Use without concomitant beta blockers is not recommended**
- Clonidine
  - 0.2 mg orally initially, followed by 0.1 mg every hour to a total of 0.8 mg, lower BP over a period of several hours
  - Sedation is frequent and rebound HTN may occur if drug is stopped

TABLE 241-9 PREFERRED PARENTERAL DRUGS FOR SELECTED HYPERTENSIVE EMERGENCIES

Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Antihypertensive Agent	Intravenous Dose
Nitroprusside	Initial 0.3 (μg/kg)/min; usual 2–4 (μg/kg)/min; maximum 10 (μg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 μg/kg over 1 min, then 50–300 (μg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 μg/min, then titrate by 5 μg/min at 3–5 min intervals; if no response is seen at 20 μg/min, incremental increases of 10–20 μg/min may be used
Hydralazine	10–50 mg at 30-min intervals

TABLE 241-7 LIFESTYLE MODIFICATIONS TO MANAGE HYPERTENSION

Weight reduction	Attain and maintain BMI < 25 kg/m^2
Dietary salt reduction	< 6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/day in men and ≤1 drink/day in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Note: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

Vasoconstrictor drugs

Vasoconstrictor drugs

- Sympathomimetic amines
  - (direct and indirect)
- Peptides
  - Angiotensin II
  - Antidiuretic Hormones (ADH) and
  - Endothelin (no clinical use)
- 5-HT_{1D} receptor agonists
  - Dihydroergotamine
  - Triptans
- Eicosanoids (thrombaxone A2)- no clinical use

Clinical uses -- vasoconstrictors

- Local application
  - Nasal decongestion
  - Coadministration with local anesthetics
- Circulatory shock
  - Sympathetic amines
- Anaphylactic shock & cardiac arrest
  - Adrenaline
- To stop esophageal bleeding in patients with portal hypertension caused by CLD
  - **ADH (**A posterior pituitary hormone**)**
  - Octreotide ---- a long acting analogue of somatostatin

Vasopressin – ADH

- **Antidiuretic action on the kidney**
  - Mediated via **V_2** receptors and involve Activation of adenylate cyclase in renal collecting ducts
  - Occurs at low plasma concentration of ADH
- **A powerful vasoconstrictor ---** generalized vasoconstriction
  - Mediated through **V_1** receptors
  - Require higher concentration and involve activation of **phospholipase C**
  - Used to treat patients with bleeding **esophageal varices and portal hypertension**
  - It also affects other smooth muscles – GIT and uterine – **abdominal cramps**