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CHAPTER

Antihypertensive Drugs

Competency covered

PH 1.27: Describe the mechanisms of action, types, doses, side effects, indications and contraindications of *antihypertensive drugs*.

Antihypertensives are drugs used to lower BP in hypertension.

Hypertension (HT) is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity. The cut-off manometric reading between normotensives and hypertensives is arbitrary. For practical purposes 'hypertension' could be that level of BP at or above which mortality / morbidity benefits of long-term intervention (lifestyle measures or drug treatment) have been demonstrated by outcome based randomized clinical trials (RCTs). Almost all updated HT management guidelines including NICE (2019), JNC8 (2014), ISH (2020), European Society of Hypertension (2023) continue to define the cut-off level to be 140 mm Hg systolic and 90 mm Hg diastolic. However, the JNC8 have raised the defining level to 150/90 mm Hg for individuals above 60 years of age. Epidemiological studies have confirmed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.

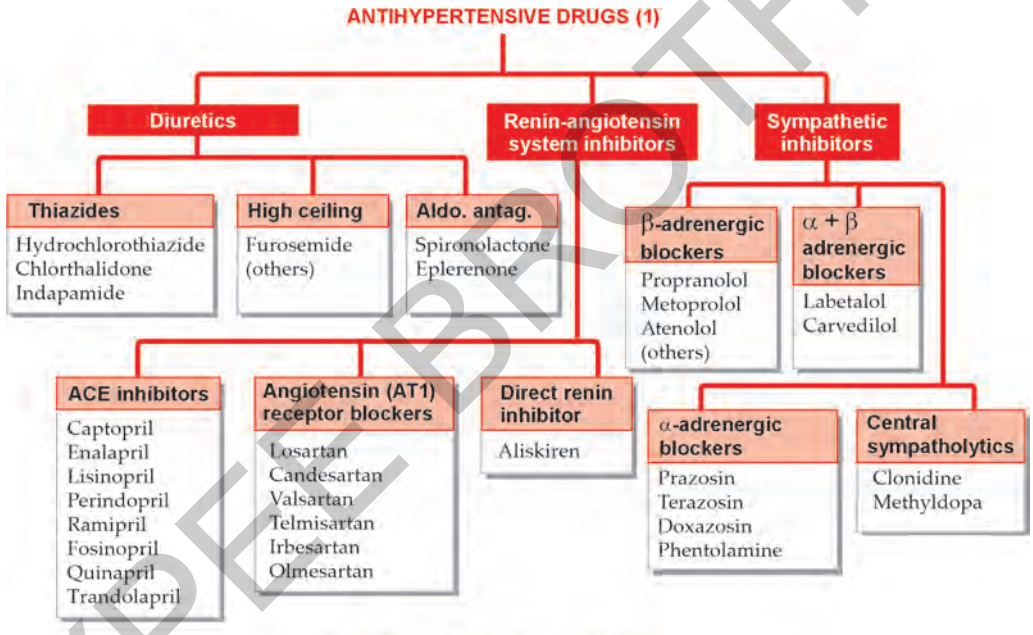
Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and renin-angiotensin systems (RAS) may or may not be overactive, but they do contribute to the tone of blood vessels and c.o. in hypertensives, as they do in normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other, while others directly reduce peripheral resistance or blood volume.

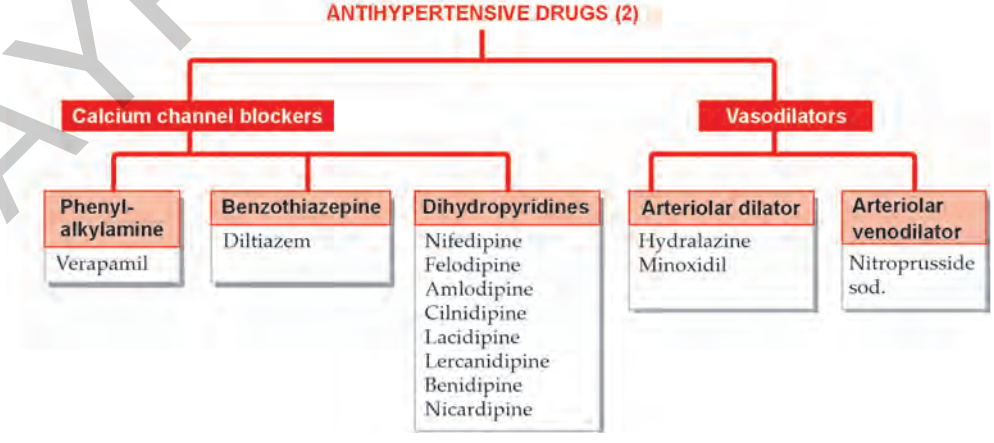
Antihypertensive drug therapy has been remarkably improved in the last 70 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive was available. *Veratrum* and *Sod. thiocyanate* could lower BP, but were toxic and difficult to use. The *ganglion blockers* developed in the 1950s were effective, but produced a variety of side effects. *Reserpine* was a breakthrough, but produced mental depression. The therapeutic potential of *hydralazine* could not be tapped fully because of marked side effects when it was used alone. The antihypertensives of the 1960–70s were *methyldopa*, β *blockers*, *thiazide* and *high ceiling diuretics* and *clonidine*.

- JNC 8 (2014): Evidence-based guideline for the management of high blood pressure in adults; report from the panel members appointed to the JNC-8 (Joint National Committee USA); 2014.
- ISH (2020): International Society of Hypertension: global hypertension practice guidelines; *Hypertension.* ***75****(6):1334-57;2020.*
- ESH (2023): European Society of Hypertension guidelines for the management of hypertension; *J. Hypertens.* **41**(12):1874-2071;2023.
- NICE (2019): National Institute for Health Care and Excellence: Hypertension in adults: diagnosis and management. NG136;2019. *https//www.nice.org.uk/guidance/ng136.*

Abbreviations

ACE : Angiotensin converting enzyme
ARB : Angiotensin receptor blocker
CAD : Coronary artery disease
CCB : Calcium channel blocker
CHF : Congestive heart failure
CKD : Chronic kidney disease
c.o. : Cardiac output
DHP : Dihydropyridine
DM : Diabetes mellitus
ESH : European Society of Hypertension
HCZ : Hydrochlorothiazide
HDL : High density lipoprotein
HT : Hypertension
ISH : Isolated systolic hypertension
JNC : Joint national committee
LDL : Low density lipoprotein
MI : Myocardial infarction
NICE : National Institute for Health and Care excellence (UK)
NSAID : Nonsteroidal anti inflammatory drug
RAS : Renin-angiotensin system
RCT : Randomized clinical trial
TOD : Target organ damage
t.p.r. : Total peripheral resistance





The status of β blockers and diuretics was consolidated in the 1970s and selective α_1 blocker *prazosin* broke new grounds. The antihypertensives introduced in the 1980–90s were angiotensin II converting enzyme *(ACE) inhibitors* and *calcium channel blockers*. Angiotensin receptor blockers (ARBs) were added soon after. With the development of many types of drugs, delineation of their long-term benefits and complications, and understanding of the principles on which to combine them, hypertension can now be controlled in most cases with minimum discomfort. Evidence-based guidelines for selection of antihypertensive drugs for different categories of patients have now been developed.

DIURETICS

Diuretics have been the standard antihypertensive drugs over the past nearly 5 decades, though they do not lower BP in normotensives. Their pharmacology is described in Ch. 41.

Thiazides Hydrochlorothiazide (HCZ) and chlorthalidone are the diuretic of choice for uncomplicated hypertension; have similar efficacy and are dose to dose equivalent. All mega-trials have been carried out with these two only. Chlorthalidone is longer acting (~ 48 hours) than HCZ (< 24 hours) and may have better round-the-clock action. It is favoured over HCZ by the NICE guidelines. Indapamide (*see* later) is also mainly used as antihypertensive, and is equally effective. Other members of the thiazide class should not be considered interchangeable with these as antihypertensive. The proposed mechanism of antihypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by 5–15%, and indirectly decreases c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na^+ balance and plasma volume; c.o. is nearly restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most probably an indirect consequence of a small (~5%) persisting Na^+ and volume deficit. Decrease in intracellular Na^+ concentration in the vascular smooth muscle may reduce stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, Ang II).

The fall in BP develops gradually over 2–4 weeks. During long-term treatment with thiazides, the heart rate and c.o. remain unaffected, while t.p.r. is reduced despite compensatory increase in plasma renin activity, which confirms persisting Na^+ deficit. Sympathetic reflexes are not impaired: postural hypotension is rare. Thiazides are mild antihypertensives, average fall in mean arterial pressure is <10 mm Hg. Monotherapy with thiazides is effective in ~30% cases. Thiazides are seldom used alone, but they potentiate all other antihypertensives (except DHPs) and prevent development of tolerance to these drugs by not allowing expansion of plasma volume. Thus, in combination, they are useful in all grades of hypertension. Diuretics are more effective in the elderly. Maximal antihypertensive efficacy is reached at 25 mg/day HCZ, though higher doses produce greater diuresis. Their antihypertensive action is attenuated by NSAIDs.

High ceiling diuretics Furosemide is a strong diuretic, but a weaker antihypertensive than thiazides. The fall in BP is entirely dependent on reduction in plasma volume and c.o. The explanation to this paradox may lie in its brief duration of action. The natriuretic action lasting only 4–6 hr after the conventional morning dose is followed by compensatory increase in proximal tubular reabsorption of Na^+. The Na^+ deficient state in vascular smooth muscle may not be maintained round-the-clock. The t.p.r. and vascular responsiveness are not reduced. Moreover, the high ceiling diuretics are more liable to cause fluid and electrolyte imbalance, weakness and other side effects. They are indicated in hypertension only when it is complicated by chronic renal failure or coexisting refractory CHF, or when fluid retaining potent vasodilators are used.

Desirable properties of thiazide diuretics as antihypertensives are:

1. Once a day dosing and flat dose-response curve permitting simple standardized regimens.
2. No fluid retention, no tolerance.
3. No postural hypotension and relative freedom from side effects, especially from CNS symptoms.

4. More effective in elderly patients and in those with isolated systolic hypertension (ISH).
5. Thiazides decrease Ca^{2+} excretion; may lower risk of osteoporosis in older women.
6. Low cost.

Current status of diuretics as antihypertensives

In the 1960–70s, thiazide diuretics were almost routinely prescribed alone or in combination, to nearly all hypertensive patients. The usual dose used was HCZ / chlorthalidone 50 mg/day. Soon a number of drawbacks were highlighted:

- Hypokalaemia—muscle pain, fatigue and loss of energy.
- Erectile dysfunction in males.
- Carbohydrate intolerance, precipitation of diabetes due to reduction of insulin release.
- Dyslipidemia: rise in total and LDL cholesterol and triglycerides with lowering of HDL which could increase atherogenic risk.
- Hyperuricaemia: by inhibiting urate excretion—increased incidence of gout.
- Increased incidence of sudden cardiac death: attributed to episodes of *torsades de pointes* and ischaemic ventricular fibrillation precipitated by hypokalaemia.

Consequently, prescribing of diuretics declined. Subsequently, several dose-ranging studies and interventional trials demonstrated that the adverse consequences of thiazide use were dose-dependent, and that 25 mg/day HCZ dose yielded the best benefit-risk ratio. Favourable outcomes obtained at ≤25 mg/day HCZ in studies, including ALLHAT (2002) and a meta-analysis (2003) have reinstated thiazide diuretics as one of the first line antihypertensives.

Findings with low dose (12.5–25 mg/day) thiazide therapy are:

- Though serum K^+ falls marginally, significant hypokalaemia does not occur; K^+ sparing diuretics are usually not needed.
- Continuous ECG recording studies failed to document increased incidence of arrhythmias.
- Impairment of glucose tolerance or increase in serum cholesterol or hyperuricaemia over long-term are minimal. Benefits of low-dose thiazides outweigh its potential to worsen diabetes. They are not contraindicated in diabetics.
- Analysis of several trials has found thiazides to reduce fatal and nonfatal MI by 27–44%. The incidence of stroke is reduced by 31–49%. Overall mortality and morbidity is reduced in long-term trials.
- Some trials in mild to moderate hypertension have found thiazides to reduce left ventricular hypertrophy.

The JNC 8, NICE, (2019) and other guidelines recommend instituting 12.5–25 mg/day thiazide therapy, with or without added K^+ sparing diuretic, as one of the first line treatment of essential hypertension, especially in the elderly if a calcium channel blocker (CCB) cannot be used. If the low dose (25 mg/day) fails to reduce BP to desired level, another antihypertensive should be added, rather than increasing dose of the diuretic. Thiazides are ineffective in patients with chronic kidney disease (CKD), and are not recommended. High-ceiling diuretics are effective in patients with CLcr 30 mg/ml or less, and may be used in place of HCZ.

Indapamide It is a mild diuretic, chemically related to chlorthalidone. It lowers BP at doses which cause little diuresis. Electrolyte disturbances, K^+ loss and metabolic effects are minimal at antihypertensive doses. The NICE guidelines favour chlorthalidone and indapamide over HCZ.

Indapamide is well absorbed orally, has an elimination t½ of 16 hr. It is well tolerated: side effects are minor g.i. symptoms and fatigue. Hypokalaemia is infrequent.

LORVAS, NATRILIX 2.5 mg tab, NATRILIX-SR 1.5 mg SR tab

Aldosterone antagonists Spironolactone and eplerenone themselves lower BP slightly. Used in conjunction with a thiazide diuretic they prevent K^+ loss and augment the antihypertensive action. Spironolactone has hormonal side effects (gynaecomastia, impotence, menstrual irregularities). This problem is offset in the newer aldosterone antagonist eplerenone, (*see* Ch. 41), which is increasingly used.

With the realization of the role of aldosterone in promoting hypertension related ventricular and

vascular hypertrophy and renal fibrosis, it is considered that aldosterone antagonists will attenuate these complications. As such, there is resurgence in their use, especially in refractory hypertension.

The NICE and JNC 8 guidelines recommend adding an aldosterone antagonist to the ACE inhibitor/ARB + CCB + thiazide triple therapy, if the target level BP is not attained and serum K^+ is ≤ 4.5 mmol/L. Hyperkalemia should be watched when aldosterone antagonists are used, particularly in combination with ACE inhibitors/ARBs.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

The ACE inhibitors are one of the first choice drugs in all grades of essential as well as renovascular hypertension (except those with bilateral renal artery stenosis). Most patients require relatively lower doses (enalapril 2.5–10 mg/day or equivalent) which are well tolerated. Used alone they control hypertension in ~50% patients, and addition of a CCB or diuretic extends efficacy to ~80%. Because of supraadditive synergism, only a low dose of diuretic (12.5 mg of HCZ, rarely 25 mg) needs to be added. The pharmacology and use of ACE inhibitors in hypertension are described in Ch. 36. Of particular mention is their renal blood flow improving action, their potential to retard diabetic nephropathy and their capacity to regress left ventricular/vascular hypertrophy. They are the most appropriate antihypertensives in patients with diabetes, nephropathy (even nondiabetic CKD), left ventricular hypertrophy, CHF, angina and post MI cases. Several large prospective studies including AIRE (1993), HOPE (2000), ALLHAT (2002) have confirmed the antihypertensive and cardioprotective effects of ACE inhibitors. They are more effective in younger (< 55 year) hypertensives than in the elderly, as well as in white races than in blacks. Dry persistent cough is the most common side effect requiring discontinuation of ACE inhibitors.

ANGIOTENSIN RECEPTOR BLOCKERS

The pharmacology of *losartan* and other ARBs is described in Ch. 36. Losartan 50 mg / day or telmisartan 40 mg/ day or equivalent dose of another ARB is an effective antihypertensive. Action manifests early and progresses to peak at 2–4 weeks. Addition of 12.5 mg/day HCZ further enhances the fall in BP. The newer ARBs—valsartan, candesartan, irbesartan and telmisartan have been shown to be as effective antihypertensives as ACE inhibitors, while losartan may be somewhat weaker than high doses of ACE inhibitors. ARBs are remarkably free of side effects. Because they do not increase kinin levels, the ACE inhibitor related cough is not encountered. Angioedema, urticaria and taste disturbance are also rare. Though effects of ACE inhibitors and ARBs are not identical, the latter have all the metabolic and prognostic advantages of ACE inhibitors.

Several interventional endpoint reduction trials like LIFE (2002), VALUE (outcomes in hypertensive patients with valsartan or amlodipine, 2004), SCOPE (study on cognition and prognosis in the elderly; stroke prevention with candesartan in elderly with isolated systolic hypertension, 2004), JLIGHT (Japanese losartan therapy intended for global renal protection in hypertensive patients, 2004) have attested to the favourable effects of ARBs on morbidity and mortality in hypertensive patients.

As antihypertensive, use of ARBs has outstripped that of ACE inhibitors. The NICE (2019) guidelines consider ARBs to be preferable over ACE inhibitors for black races. Both JNC8 and NICE recommend not to combine ACE inhibitors with ARBs for hypertension.

DIRECT RENIN INHIBITOR

Aliskiren is the only available member of the latest class of RAS inhibitors which act by blocking catalytic activity of renin and inhibiting production of Ang I and Ang II. It is described in Ch. 36. Aliskiren is an equally effective antihypertensive as ACE inhibitors and ARBs, but experience with it so far is limited. However, no remarkable features have emerged, and presently it is to be employed only when the more established ACE inhibitors or ARBs cannot be used.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. Their pharmacology is described in Ch. 39. All 3 subgroups of CCBs, *viz.* dihydropyridines

(DHPs), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives, but DHPs are mainly used. Amlodipine is the most popular DHP antihypertensive in India. The DHPs lower BP by decreasing peripheral resistance without compromising c.o. Despite vasodilatation, tachycardia and fluid retention are insignificant.

Ankle edema that occurs in some recipients is due to increased hydrostatic pressure across capillaries of the dependent parts as a result of reflex constriction of post capillary vessels in these vascular beds.

The onset of antihypertensive action is quick. With the availability of long acting preparations, most agents can be administered once a day. Short acting CCBs / formulations (nifedipine regular formulation) are not used to treat hypertension. Monotherapy with CCBs is effective in upto 60% hypertensives, and DHPs may improve arterial compliance. Combined with other drugs, they are effective in all grades of hypertension, and in all ethenic groups. Other advantages of CCBs are:

1. Do not compromise haemodynamics: no impairment of physical work capacity.
2. No sedation or other CNS effects; cerebral perfusion is maintained.
3. Not contraindicated in asthma, angina (especially variant) and PVD patients: may benefit these conditions.
4. Are particularly effective in elderly patients, black races and in low renin hypertensives.
5. Do not affect male sexual function.
6. No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.
7. Shown to have no / minimal effect on quality of life.
8. No adverse foetal effects; CCBs can be used during pregnancy.

Some large controlled trials including ASCOT-BPLA (2005) and ACCOMPLISH (2008) have testified to superior efficacy of amlodipine both as monotherapy and when combined with an ACE inhibitor for reducing cardiovascular events in high risk hypertensive patients. Thus, CCBs continue to be used as one of the first line monotherapy options (JNC8-2014, NICE-2019, ISH-2020 guidelines) because of their high efficacy and excellent tolerability. Moreover, there is convincing evidence of their stroke preventing potential (syst EUR, ALLHAT studies). The long-acting DHPs are next to ACE inhibitors in reducing albuminuria and slowing disease progression in hypertensive / diabetic nephropathy. They are the most useful antihypertensives in *cyclosporine induced hypertension* in renal transplant recipients.

β-ADRENERGIC BLOCKERS

The pharmacology and mechanism of antihypertensive action of β blockers is described in Ch. 11. They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in ~30 patients—mostly stage I cases.

The hypotensive response to β blockers develops over 1–3 weeks and is then well sustained. Despite short and differing plasma half lives, the antihypertensive action of most β blockers is maintained over 24 hr with a single daily dose.

All β blockers, irrespective of associated properties, exert equivalent antihypertensive effect. Nebivolol lowers t.p.r. by enhancing endothelial NO production, and carvedilol does so by blocking α_1 receptors as well. These vasodilating β blockers are being preferred by many experts.

There are several contraindications to β blockers, including cardiac, pulmonary and peripheral vascular disease. The nonselective β blockers have an unfavourable effect on lipid profile (they raise triglyceride level and LDL/HDL ratio). They have also fared less well on quality of life parameters like decreased work capacity, fatigue, loss of libido and subtle cognitive effects (forgetfulness, low drive), nightmares and increased incidence of antidepressant use. Many of these drawbacks are minimized in the β_1 selective agents and in those which penetrate brain poorly. However, some recent studies have pointed out that atenolol monotherapy may be less effective in preventing hypertension related stroke and coronary artery disease.

β blockers and ACE inhibitors are the most effective drugs for preventing sudden cardiac death in postinfarction patients. However, β blockers are

less effective for primary prophylaxis of MI and for preventing left ventricular hypertrophy, though all-cause mortality has been decreased in long-term trials. Hypertensive subjects with stable heart failure should be treated with one of the selected β blockers (metoprolol-SR / bisoprolol / carvedilol / nebivolol) along with an ACE inhibitor / ARB (CIBIS, 1999; MERIT-HF, 1999, COPERNICUS, 2002 studies). Barring the above subsets of patients with compelling indications and suitability criteria, β blockers are not selected now as the initial antihypertensive. β blockers are considered less effective and less suitable for the elderly hypertensive patients. The LIFE (2002) and ALLHAT (2002) trials have found β blockers to be inferior to low-dose thiazide or ACE inhibitor / ARB or a combination of these in preventing stroke, as well as in diabetic patients. As monotherapy, ACE inhibitors/ARBs and CCBs compromise quality of life less than β blockers. Rebound hypertension has occurred on sudden discontinuation of β blockers; myocardial ischaemia may be aggravated and angina or MI may be precipitated.

Mainly due to inferior efficacy in primary prevention of MI and stroke, as well as other drawbacks pointed out above, *β blockers are no longer considered first line antihypertensive drugs* for monotherapy, except in patients with other compelling indications such as concurrent angina pectoris, stable heart failure or migraine. They are mostly used now as add-on drug to triple therapy of resistant hypertension (JNC-8 2014, NICE 2019 and ISH 2020 guidelines).

β+α ADRENERGIC BLOCKERS

Labetalol (*see* Ch. 11). It is a combined α and β blocker; reduces t.p.r. and acts faster than pure β blockers. It has been used i.v. for rapid BP reduction in hyperadrenergic states, cheese reaction, clonidine withdrawal, eclampsia, etc. (*see* p. 633). Oral labetalol therapy is restricted to moderately severe hypertension not responding to a pure β blocker, because side effects of both α blocker and β blocker occur with it. Labetalol is a preferred antihypertensive for rise in BP due to preeclampsia.

Carvedilol This nonselective β + weak selective α_1 blocker produces vasodilatation and has additional antioxidant / free radical scavenging properties. Whether these ancillary properties confer any superiority is not known. Carvedilol is a frequently selected drug for long-term treatment of CHF, and is approved as an antihypertensive as well. Side effects are similar to labetalol; liver enzymes may rise in some.

α-ADRENERGIC BLOCKERS

Prazosin (*see* Ch. 11)

This prototype selective α_1 antagonist dilates both resistance and capacitance vessels; effect on the former predominating. The haemodynamic effects, *viz* reduction in t.p.r. and mean BP accompanied by minor decrease in venous return and c.o. are similar to that produced by a direct acting vasodilator hydralazine. However, unlike hydralazine, there is little reflex cardiac stimulation and renin release during long-term therapy. Tachycardia does not compensate for the fall in BP, because release inhibitory α_2 (presynaptic) receptors are not blocked: autoregulation of NA release remains intact.

Renal blood flow and g.f.r. are maintained but fluid retention may attend fall in BP cardiovascular reflexes are not appreciably impaired during chronic therapy, but postural hypotension and fainting may occur in the beginning—called 'first dose effect', and with dose increments. This disappears with continued therapy, but may persist in the elderly. For this reason, prazosin is always started at low dose (0.5 mg) given at bedtime and gradually increased with twice daily administration till an adequate response is produced (max. dose 10 mg BD). An oral dose produces peak fall in BP after 4–5 hours and the effect lasts for nearly 12 hours, though plasma t½ is only 3 hours. This may be due to generation of active metabolites.

Prazosin does not impair carbohydrate tolerance, and may have a small favourable effect on lipid profile. Symptomatic improvement may occur in males with urinary symptoms due to prostatic hypertrophy.

MINIPRESS XL: Prazosin GITS 2.5 mg, 5 mg tabs.; PRAZOPRESS 1, 2 mg tabs.

Adverse effects Prazosin is generally well tolerated at low doses. Apart from postural hypotension related symptoms (particularly in the beginning), other side effects are headache, drowsiness, dry mouth, weakness, palpitation, nasal blockade, blurred vision and rash. Ejaculation may be impaired in males: especially with higher doses. Fluid retention attending prazosin monotherapy may precipitate CHF.

Use Prazosin is a moderately potent antihypertensive, but is not used as a first line drug because fluid retention and tolerance gradually develops with monotherapy—necessitating dose increase—more side effects and risk of CHF. It may be added to the triple drug regimen of ACE inhibitor / ARB + diuretic + CCB in those not achieving target BP (NICE 2019).

Terazosin, Doxazosin These are long-acting congeners of prazosin with similar properties but suitable for once daily dosing (*see* p. 172). In the ALLHAT (2002) study doxazosin monotherapy has doubled the incidence of CHF and more patients suffered stroke compared to those receiving a diuretic; but this can occur with any α_1 blocker.

Nonselective α blockers (Phentolamine, Phenoxybenzamine)

The nonselective α blockers have been disappointing for routine treatment of hypertension, because fall in t.p.r. is compensated by increased HR and c.o. This is due to blockade of presynaptic α2 receptors resulting in augmentation of NA release. They are reserved for special situations like pheochromocytoma, clonidine withdrawal, cheese reaction, etc., where circulating CAs are responsible for the rise in BP.

CENTRAL SYMPATHOLYTICS

Clonidine It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α_2 receptors, especially α_{2A} subtype in brainstem. The major haemodynamic effects result from stimulation of α_{2A} receptors present in medulla (vasomotor centre) which decreases sympathetic out flow resulting in fall in BP and bradycardia. Enhanced vagal tone also contributes to the bradycardia. Plasma NA declines. Though clonidine is capable of reducing NA release from peripheral adrenergic nerve endings (release inhibitory prejunctional α_2 action), this is not manifest at clinically used doses. Clonidine is a moderately potent antihypertensive.

Pharmacokinetics Clonidine is well absorbed orally; peak occurs in 2–4 hours; 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

Dose: Start with 100 µg OD or BD, max. 300 µg TDS, orally. CATAPRES 150 µg tab, ARKAMIN 100 µg tab.

Adverse effects Side effects with clonidine are relatively common.

- Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes (secretion is decreased by central action), constipation (antisecretory effect on the intestines).
- Impotence, salt and water retention, bradycardia.
- Postural hypotension occurs, but is mostly asymptomatic.
- Alarming rise in BP, in excess of pretreatment level, with tachycardia, restlessness, anxiety, sweating, headache, nausea and vomiting occur in some patients when doses of clonidine are missed for 1–2 days. The syndrome is very similar to that seen in pheochromocytoma: plasma catecholamine (CA) concentration is increased. This is due to:
  (a) Sudden removal of central sympathetic inhibition resulting in release of large quantities of stored CAs.
  (b) Supersensitivity of peripheral adrenergic structures to CAs that develops due to chronic reduction of sympathetic tone during clonidine therapy.

A combination of α blocker with a β blocker, or a potent vasodilator (nitroprusside) or clonidine itself can be used to treat the syndrome.

Interactions Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine, probably by blocking α receptors on which clonidine acts.

Use Clonidine was a popular antihypertensive in the late 1960s and 1970s, but frequent side effects, risk of withdrawal hypertension and development of tolerance have relegated it to a 3rd or 4th line drug. There is no data on prognostic benefits, of clonidine. At present, it is occasionally used to supplement the first line antihypertensive drugs.

Other indications

1. Opioid withdrawal: Opioid and α_2 adrenergic systems converge on the same effectors in many systems; both activate the Gi regulatory protein. Clonidine suppresses sympathetic overactivity of opioid withdrawal syndrome and reduces craving to some extent.

   Clonidine has also facilitated alcohol withdrawal and smoking cessation.
2. Clonidine has analgesic activity. It has been used to substitute morphine for intrathecal / epidural surgical and postoperative analgesia.
3. Clonidine attenuates vasomotor symptoms of menopausal syndrome.

Methyldopa This α-methyl analogue of dopa is converted in the body to α methyl NA, which is a selective α_2 agonist. In the brain, the α methyl NA generated from methyldopa acts on central α_2 receptors to decrease efferent sympathetic activity. However, in contrast to clonidine, methyldopa decreases t.p.r. more than HR and c.o.

Methyldopa is a medium efficacy antihypertensive. Circulating levels of NA and renin tend to decrease due to reduction in sympathetic tone. Inhibition of postural reflexes is mild.

Pharmacokinetics Though methyldopa is transported actively by intestinal amino acid carrier, less than 1/3 of an oral dose is absorbed. It is partly metabolized and partly excreted unchanged in urine. Antihypertensive effect develops over 4–6 hours and lasts for 12–24 hours.

Dose: 0.25–0.5 g BD–QID oral.

EMDOPA, ALPHADOPA 250 mg tab.

Adverse effects Sedation, lethargy and reduced mental capacity are common side effects. Cognitive impairment may develop. Dryness of mouth, nasal stuffiness, headache, fluid retention, weight gain and impotence are the other side effects.

Postural hypotension is generally mild.

Positive Coomb's test occurs in 1/6 patients, but few develop haemolytic anaemia. Fever, rash, hepatitis, 'flu' like illness, thrombocytopenia and rarely lupus syndrome occur.

Rebound hypertension on sudden withdrawal of methyldopa is mild and less common.

Interactions Tricyclic antidepressants reverse its action by blocking its active transport into the adrenergic neurones.

Use Methyldopa was a widely used antihypertensive in the 1960s and 1970s, especially in combination with a diuretic. However, it is rarely used now, except to treat hypertension during pregnancy wherein it has a long track record of safety, both for the mother as well as for the foetus.

VASODILATORS

Hydralazine/Dihydralazine Introduced in the 1950s, it is a directly acting arteriolar vasodilator with little action on venous capacitance vessels. Hydralazine reduces t.p.r. and causes greater decrease in diastolic than in systolic BP. Reflex compensatory mechanisms are evoked which cause tachycardia, increase in c.o. and renin release → increased aldosterone production, which causes Na^+ and water retention. Thus, a hyperdynamic circulatory state is induced—angina may be precipitated due to increased cardiac work. There is no reduction in renal blood flow despite fall in BP. However, fluid retention and edema develop by the above mechanism. Tolerance to the hypotensive action of hydralazine develops unless a diuretic or a β blocker or both are given together to counteract the compensatory mechanisms.

The mechanism of vascular smooth muscle relaxant action of hydralazine is not clearly known. Interference with Ca^{2+} release, opening of certain K^+ channels and/or NO generation may be involved.

Pharmacokinetics Hydralazine is well absorbed orally, and is subjected to first pass metabolism in liver. The chief metabolic pathway is acetylation which exhibits a bimodal distribution in the population: there are slow and fast acetylators.

Hydralazine is completely metabolized both in liver and plasma; the metabolites are excreted in urine, $t_{½}$ is 1–2 hours. However, hypotensive effect lasts longer (12 hours), probably because of its persistence in the vessel wall.

Dose: 25–50 mg OD–TDS; NEPRESOL 25 mg tab.

Adverse effects are frequent and mainly due to vasodilatation.

- Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
- Angina and MI may be precipitated in patients with coronary artery disease.
- Postural hypotension is not prominent because of little action on veins.
- Paresthesias, tremor, muscle cramps, rarely peripheral neuritis. Gastrointestinal disturbances are frequent.
- Lupus erythematosus or rheumatoid arthritis like symptoms develop on prolonged use of doses above 100 mg/day. This is more common in women and in slow acetylators.

Use Hydralazine is now rarely used as a second line alternative drug only in combination with a diuretic and β blocker for patients not achieving target BP with first line drugs. It is one of the antihypertensives that has been safely used during pregnancy, especially for preeclampsia. Injected hydralazine is occasionally employed in hypertensive emergencies. It is contraindicated in older patients and in those with ischaemic heart disease.

The arteriolar dilator action of hydralazine can be utilized in the management of CHF particularly in combination with isosorbide dinitrate (*see* p. 582).

Minoxidil It is a powerful vasodilator, the pattern of action resembling hydralazine. Vasodilator side effects are more marked; risk of cardiac ischaemia and heart failure is high. Therefore, it is not used orally now.

The active metabolite of minoxidil is an opener of ATP sensitive K^+ channels; causes vasodilatation by hyperpolarizing smooth muscle.

Use in alopecia Hirsutism was observed as a side effect of oral minoxidil. Applied topically (2% twice daily) it promotes hair growth in *male pattern baldness* and in *alopecia areata*. The response is slow (takes 2–6 months) and incomplete, but upto 60% subjects derive some benefit, albeit for short periods. Baldness recurs when application is discontinued. The mechanism of increased hair growth is not known; may involve:

(a) Opening of K^+ channels and improved microcirculation around hair follicles.
(b) Direct stimulation of resting hair follicles.
(c) Alteration of androgen effect on genetically programmed hair follicles.

Local irritation, itching and burning sensation are frequent. Dermatological reaction and systemic side effects (headache, dizziness, palpitation) occur in 1–3% cases.

MINTOP, GROMANE 2% scalp lotion, MULTIGAIN 2% topical solution and metered spray, MANEXIL 5% gel; apply twice a day.

Sodium nitroprusside It is a rapidly (within seconds) and consistently acting vasodilator with brief duration of action (2–5 min) so that vascular tone can be titrated with the rate of i.v. infusion. Nitroprusside dilates both resistance and capacitance vessels: reduces t.p.r. as well as c.o. (by decreasing venous return). Myocardial work is reduced, but ischaemia may be accentuated due to coronary steal. Only mild reflex tachycardia is produced in supine posture. Plasma renin is increased.

In patients with heart failure and ventricular dilatation, nitroprusside improves ventricular function and c.o. mainly by reducing aortic impedance (afterload), but also by lowering atrial filling pressure (preload).

Endothelial cells, RBCs (and may be other cells) split nitroprusside to generate NO which relaxes vascular smooth muscle. The enzymes involved are different from those that produce NO from glyceryl trinitrate. Nonenzymatically, it is converted to NO and cyanide by glutathione. This may be responsible for the different pattern of vasodilator action compared to nitrates, as well as for the fact that no nitrate like tolerance develops to nitroprusside action.

Nitroprusside is now a second line drug for certain hypertensive emergencies (*see* p. 633); 50 mg is added to a 500 ml bottle of saline / glucose solution. The infusion is started at 0.02 mg/min and titrated upward with the response: 0.1–0.3 mg/min is often needed.

Nitroprusside is split to release cyanide. The latter is converted in the liver to thiocyanate which is excreted slowly. If larger doses are infused, excess thiocyanate may accumulate and produce toxicity, including psychosis and other CNS effects. Intracranial pressure may rise.

Side effects mainly due to vasodilatation are—palpitation, nervousness, vomiting, perspiration, pain in abdomen, weakness, disorientation, and lactic acidosis (caused by the released cyanide).

Nitroprusside has also been used to produce controlled hypotension, in refractory CHF (*see* p. 582) and in acute mitral regurgitation.

SONIDE, PRUSIDE, NIPRESS 50 mg in 5 ml inj.

TREATMENT OF HYPERTENSION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to the target level, with minimum inconvenience to the patient. Both systolic and diastolic BP predict the likelihood of target organ damage (TOD) and complications such as:

- Cerebrovascular disease, transient ischaemic attacks, stroke, encephalopathy.
- Hypertensive heart disease—left ventricular hypertrophy, heart failure.
- Coronary artery disease (CAD), angina, myocardial infarction (MI), sudden cardiac death.
- Arteriosclerotic peripheral vascular disease, retinopathy.
- Dissecting aneurysm of aorta.
- Glomerulopathy, renal failure.

Patients who have already suffered some TOD have greater risk of further organ damage and death at any level of raised BP, than those without TOD.

The current NICE guidelines (2019) have graded hypertension as:

	BP	
Hypertension	*Systolic*	*Diastolic*
Stage I	140–159	90–99
Stage II	160–179	100–119
Severe	≥ 180	≥ 120

Since the risk of complications depends not only on the level of BP, but also on other risk factors (*see* box) and existing TOD, these have also to be considered in selection of drugs and in devising therapeutic regimens.

Cardiovascular risk factors
1. Age > 55 years (men), > 65 years (women)
2. Family h/o premature CV disease
3. Smoking
4. Dyslipidemia (↑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

CKD–Chronic kidney disease.

The JNC have also identified compelling indications (*see* box) which may mandate use of specific antihypertensive drugs even in patients with BP values lower than 140/90 mm Hg. Moreover, presence of co-morbidities may suggest fixing a lower target BP value (<130 mm Hg systolic and <90 mm Hg diastolic) to be attained by drug therapy.

Beneficial effect of lowering BP has been established in all patients having BP above 140/90 mm Hg, and even in the 120–139 (systolic) or 80–89 mm Hg (diastolic) range in those with co-morbidites or cardiovascular risk factors; e.g. in diabetics, lowering diastolic BP to 80 mm Hg was found to reduce cardiovascular events to a greater extent than on reducing it upto 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 drug 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 age.

Data from several large studies has shown that effective use of antihypertensive drugs reduces occurrence of stroke by 30–50%, heart failure by 40–50% and coronary artery disease (CAD) by ~15%.

If the cause of hypertension can be identified (hormonal, vascular abnormality, tumour, renal disease, drugs) all efforts should be made to remove it. Nonpharmacological measures (lifestyle modification—diet, Na^+ restriction, aerobic activity or exercise, weight reduction, moderation in alcohol intake, mental relaxation, etc.) should be tried first and concurrently with drugs. When significant cardiovascular and/or renal damage has already occurred, lowering BP to normotensive level may not be tolerated: edema, CHF, angina, rise in blood urea and syncope may be precipitated. Therefore, BP reduction should be gradual and only to the level tolerated.

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. Hypertensive / Diabetic nephropathy
2. Stroke prevention
β-Adrenergic blockers
1. Stable heart failure
2. Post-myocardial infarction
3. High coronary artery disease risk

There is some recent evidence (from HYGIA chronotherapy trial 2020, conducted in >19000 hypertensives and followed up for a median of 6.3 years) that ingestion of one or more antihypertensive medications at bed time significantly diminished occurrence of major cardiovascular events, compared to the conventional ingestion of all the drugs upon waking. There was also a lower incidence of nocturnal BP dipping in the bed time dosing group.

Selection of antihypertensive drug / combination of drugs

In the past, evaluation of thiazide diuretics, β 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 (JNC 8, NICE 2011, 2019) have excluded β 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 described on p. 624–25.

A **stepped care approach**, initially using a single drug and progressively adding one or more drugs from different groups according to need, is recommended by most experts and therapeutic guidelines.

Step 1 The drug to initiate therapy is selected on the basis of compelling indications of which type 2 diabetes mellitus (DM) is a decisive comorbidity, since ACE inhibitors / ARBs are the best option in diabetes. In addition, *age* and *race* has been recognized as valid basis for selecting the initial medication. According to NICE (2019) guidelines, the initial drug for all diabetic-hypertensives, irrespective of age or race should be an ACE inhibitor or ARB (*see* Fig. 40.1). In case of nondiabetics, because younger (<55 years) nonblack / Non-Caribbean origin subjects (whites and all others) generally have higher plasma renin activity and respond better to ACE inhibiters / ARBs, the initial drug should again be one of these. On the other hand, all older (≥55 years) patients and Blacks / Caribbean origin subjects of any age have lower renin status, and show a weaker response to ACE inhibitors / ARBs. Accordingly, one of the CCBs (mostly a long acting DHP, like amlodipine) is the most suitable drug. Since thiazide diuretics, even in low doses (12.5–25 mg/day), have an adverse (though minimal) metabolic profile, the NICE guidelines recommend only ACE inhibitor/ARB for young patients, and CCB for older patients as well as for all Blacks / Caribbeans. Diuretics may be used as alternatives to CCBs in patients not tolerating CCBs and in those with edema or heart failure. In women with child bearing potential and in those young hypertensives who have another contraindication to ACE inhibitor/ ARB or are intolerant to these drugs, a β blocker may be used as the initial drug.

Step 2 When the target BP is not attained by a single drug, a combination of two drugs *viz.* ACE inhibitor / ARB + CCB is used for both diabetics and nondiabetics, while a thiazide diuretic is an alternative drug for those patients in whom ACE inhibitor / ARB or CCB is not suitable or not tolerated, irrespective of the age or race of the patient. In selected cases, where therapy has been initiated with a β blocker, the second drug should be a CCB. Combination of β 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 target BP. To simplify, other guidelines recommend starting with a combination of two drugs when systolic BP is >160 mm Hg or diastolic BP is >100 mm Hg.

Step 3 The step 3 treatment includes all 3 first line drug classes, *viz.* ACE inhibitor/ARB + CCB + thiazide 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 2019 has recommend adding a fourth drug, which can either be an aldosterone antagonist (if serum K^+ is < 4.5 mmol/L) or a β blocker (especially one with vasodilating property, *viz.* carvedilol / nebivolol) or a selective α_1 blocker when serum K^+ is > 4.5 mmol / L.

Only few patients are likely to still remain uncontrolled. They require further evaluation and possible use of reserve drugs.

Antihypertensive combinations to be avoided

1. An α or β adrenergic blocker with clonidine: apparent antagonism of clonidine action has been observed.
2. Hydralazine with a DHP or prazosin; because of similar pattern of haemodynamic action.
3. Verapamil or diltiazem with β blocker, because marked bradycardia, A-V block can occur.

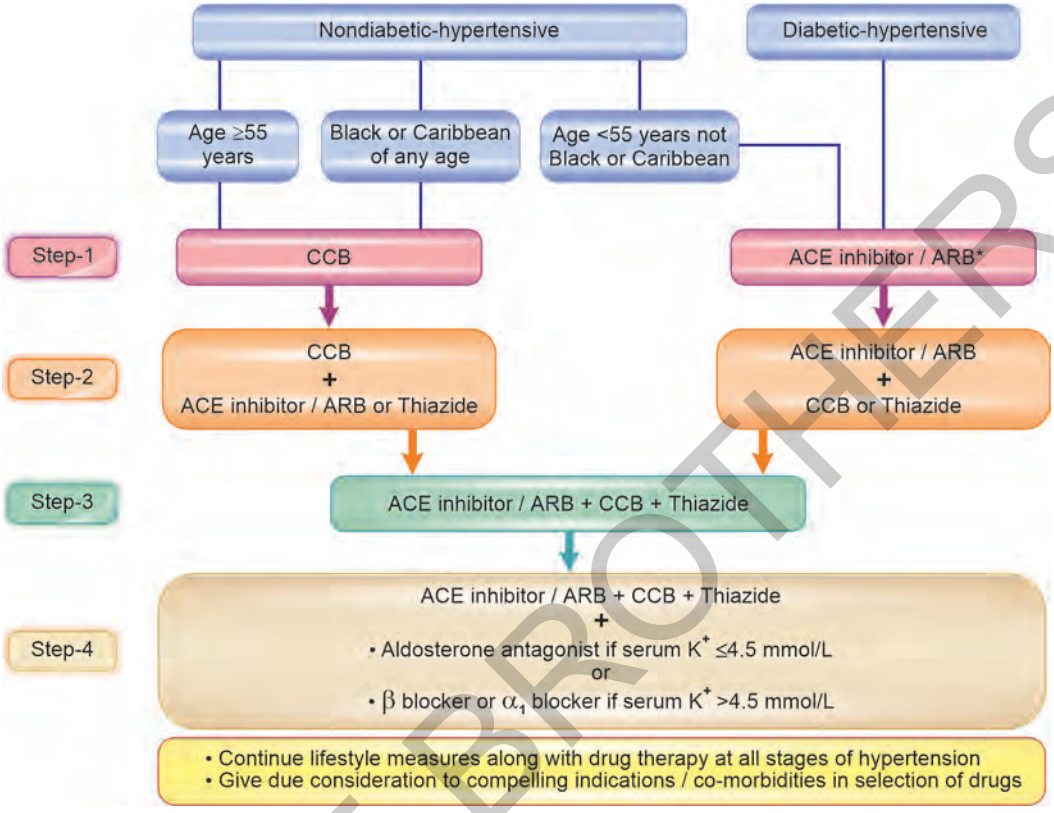


Fig. 40.1: Scheme of stepwise drug treatment of hypertension (based on NICE 2019 guidelines).
*Consider ARB in preference to ACE inhibitor in Black (African) and Caribbean origin adults.
ACE—Angiotensin converting enzyme; ARB—Angiotensin receptor blocker; CCB—Calcium channel blocker
Note: The stepwise scheme advocated by International Society of Hypertension (ISH 2020) is very similar, except that in step 1 they advise a dual low-dose drug combination (ACE inhibitor / ARB + CCB) in place of monotherapy.

4. Methyldopa with clonidine or any two drugs of the same class.
5. β blocker with diuretic, because of increased risk of developing diabetes.

Some antihypertensive combinations

1. Amlodipine 5 mg + Lisinopril 5 mg—AMLOPRES-L, LISTRIL-AM
2. Amlodipine 5 mg + Atenolol 50 mg—AMCARD-AT, AMLOPIN-AT, AMLOPRES-AT
3. Amlodipine 5 mg + Enalapril 5 mg—AMACE, AMTAS-E
4. Atenolol 25 mg or 50 mg + chlorthalidone 12.5 mg—TENOCLOR, TENORIC
5. Enalapril 10 mg + Hydrochlorothiazide 25 mg—ENACE-D, VASONORM-H
6. Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg—CARDACE-H
7. Losartan 50 mg + Hydrochlorothiazide 12.5 mg—LOSAR-H, TOZAAR-H, LOSACAR-H
8. Lisinopril 5 mg + Hydrochlorothiazide 12.5 mg—LISTRIL PULS, LISORIL-5 HT
9. Losartan 50 mg + Ramipril 2.5 mg or 5 mg—TOZAAR-R
10. Losartan 50 mg + Amlodipine 5 mg—AMCARD-LP, AMLOPRESS-Z, LOSACAR-A
11. Losartan 50 mg + Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg—LOSANORM-HR
12. Irbesartan 150 mg + Hydrochlorothiazide 12.5 mg—IROVEL-H, XARB-H.

When the BP has been well controlled for > 1 year, stepwise reduction in dose and/or withdrawal of one or more components of a combination may be attempted to workout a minimal regimen that will maintain the target BP. However, in most patients of essential hypertension, drug therapy is usually life-long.

Hypertension in pregnancy A sustained BP reading above 140/90 mm Hg during pregnancy

has implications both for the mother and the foetus. Reduction of BP clearly reduces risks. Two types of situations are possible:

(a) A woman with preexisting chronic hypertension becomes pregnant.
(b) Pregnancy related hypertension: as in toxaemia of pregnancy, *viz.* preeclampsia: BP rises after 20 weeks of gestation.

Toxaemic hypertension is associated with a hyperadrenergic state, decrease in plasma volume (despite edema) and increase in vascular resistance.

In the first category, the same therapy instituted before pregnancy may be continued. However, one of the 'safer' drugs listed below may be substituted if one of the 'drugs to be avoided' was being used. The BP should be gradually reduced to a target level of <150 mm Hg systolic and 90–100 mm Hg diastolic, but drastic reduction should be avoided, because this may impair uteroplacental blood flow.

Women with diabetes, CKD, chronic hypertension and history of rise in BP during earlier pregnancy are at higher risk of developing preeclampsia. To reduce the risk *aspirin* (80–100 mg/day) should be given from the 12th week of gestation till the baby is born. Aspirin is believed to prevent toxaemia by inhibiting TXA_2 synthesis, which presumably plays a causative role.

Antihypertensives to be avoided during pregnancy

ACE inhibitors, ARBs: Risk of foetal damage, growth retardation.

Nonselective β blockers: Propranolol has been implicated to cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.

Sod. nitroprusside: Contraindicated in eclampsia.

Antihypertensives for use during pregnancy

Labetalol This combined α + β adrenergic blocker (*see* p. 181) given orally is effective in majority of cases, and is most widely used now for hypertension during pregnancy.

Nifedipine (sustained release) This dihydropyridine CCB is a vasodilator that has been used in preeclampsia with good results. However, it should be stopped before labour begins, because it may weaken uterine contractions.

Methyldopa It has the longest record of use during pregnancy with safety, and is still used. A positive Coomb's test may occur, but has no adverse implication.

Hydralazine This old vasodilator has been safely used during pregnancy, but is not favoured now.

Hypertensive emergencies and urgencies

Systolic BP > 220 mm Hg or diastolic BP > 120 mm Hg with evidence of active target organ damage (TOD) is labelled '*hypertensive emergency*', while the same elevation of BP with symptoms, but no signs of acute TOD is termed '*hypertensive urgency*'. Severity and rate of progress of multiple TOD determines the seriousness of the condition, and the approach to drug therapy.

Controlled reduction of BP over minutes (in emergencies) or hours (in urgencies) is required to counter threat to organ function and life in the following situations:

1. Cerebrovascular accident (haemorrhagic or ischaemic stroke) or head injury with high BP.
2. Hypertensive encephalopathy (headache, confusion, irritability, disorientation, mental deterioration). It is due to spasm of cerebral vessels.
3. Hypertensive acute LVF and pulmonary edema.
4. Acute coronary syndrome (ACS) or MI with raised BP.
5. Dissecting aortic aneurysm.
6. Acute renal failure with raised BP.
7. Eclampsia.
8. Hypertensive episodes in pheochromocytoma, cocaine use, cheese reaction or clonidine withdrawal.

Parenteral drugs

Hypertensive emergencies require aggressive parenteral (preferably i.v.) therapy. Mean BP should be lowered by upto 25% over a period of minutes or may be 1–2 hours, and then more gradually to not lower than 160/100 mm Hg. If the BP is reduced too quickly or too drastically, perfusion of vital organs may suffer leading

to impairment of kidney function, myocardial ischaemia, cerebral infarction, blindness, etc. Intravenous drugs with fast, predictable, titratable and short lasting action are therefore required. Vasodilators acting directly on vascular smooth muscle (dihydropyridine CCBs, nitrodilators) and adrenergic blockers (labetalol, esmolol) meet these requirements best. Concurrent use of *nicardipine* and *labetalol* / *esmolol* is useful in most types of hypertensive emergencies.

1. Nicardipine This is one of the few DHPs available for parenteral (i.v.) use, and has become the most popular drug for a variety of hypertensive emergencies, replacing nitroprusside. Nicardipine is highly vasoselective; primarily dilates arterioles. As such reflex tachycardia may attend the fall in BP, to offset which a β blocker like esmolol or labetalol should be coadministered when it is used in hypertensive emergencies attending MI or ACS.

Nicardipine is a short acting DHP with rapid onset and offset of hypotensive effect after i.v. infusion. The fall in BP is predictable and dose related. The elimination t½ on i.v. infusion is 45 min and action lasts for 3–4 hours. In clinical trials, i.v. nicardipine was as effective as nitroprusside in lowering BP in severe hypertension. The target BP level was reached within 1 hour in >90% cases with both the drugs. Nicardipine has been found beneficial in both ischaemic as well as haemorrhagic stroke with raised BP. Its usefulness has been demonstrated in aortic dissection, acute heart failure and acute renal failure due to markedly raised BP, as well as in preeclampsia.

Nicardipine infused i.v. is better tolerated and less toxic than nitroprusside. Adverse effects of nicardipine are mostly due to vasodilatation, and are nonserious.

Dose: Initially 5 mg/hour i.v. infusion, increase rate of infusion as needed upto 15 mg/hour.

NICARDIPINE HCl 25 mg/10 ml inj.

Nicardipine has also been used in hypertension attending cardiac surgery and neurosurgery, as well as to facilitate percutaneous coronary intervention.

2. Labetalol Unlike pure β blockers, this combined β and α adrenergic blocker is an efficacious hypotensive when injected i.v. (*see* p. 181, 625), and carries low risk of causing excessive hypotension. It is particularly useful in lowering BP during episodes of rise in BP in pheochromocytoma and other hyperadrenergic states, e.g. cheese reaction, cocaine abuse, etc. Labetalol has been safely used in severe hypertension complicating aortic dissection, MI and other ACS, ischaemic stroke, intracranial haemorrhage and preeclampsia. It is good for patients with altered mental function, because it does not cause sedation or increase intracranial pressure. However, heart failure and asthma preclude its use.

Dose: 20–40 mg i.v. every 10 min till response or 20 mg/hour i.v. infusion, increased up to 120 mg/hour.

LABESOL, LABETA 20 mg/amp. and 100 mg/amp. inj.

3. Esmolol This short acting selective β_1 blocker (*see* p. 179) given as 0.5 mg/kg bolus i.v. injection followed by 50–200 µg/kg/min i.v. infusion acts in 1–2 min, and the action lasts till 10–20 min after infusion is terminated. Esmolol is particularly useful when cardiac contractility and work is to be reduced, such as in aortic dissection. Nicardipine is given concurrently because its BP lowering action is weak. In MI/ACS complicated by raised BP and tachycardia, esmolol can be usefully combined with nicardipine or GTN. It needs to be avoided in presence of systolic heart failure or asthma.

MINIBLOCK 100 mg/10 and 250 mg/10 ml inj.

4. Glyceryl trinitrate (GTN) Infused i.v. (5–20 µg/min) GTN acts within 2–5 min, but is not a potent hypotensive. Due to its predominant venodilator action, it is particularly suitable for use in MI or other ACS (*see* p. 604) and in acute heart failure accompanied by rise in BP. However, for any substantial lowering of BP, it needs to be combined with i.v. labetalol or i.v. nicardipine. Tolerance tends to develop to GTN action if it is continuously infused for >12 hours. GTN needs to be avoided in severe hypertension with ischaemic or haemorrhagic stroke.

5. Sodium nitroprusside (see p. 628) Because of instantaneous, potent and combined arteriovenous vasodilatory action, nitroprusside has been a commonly used drug for hypertensive emergencies. However, availability of less toxic and more manageable drugs has highly restricted its use. It may be used as an alternative to nicardipine in cases of aortic dissection, where it is combined with the short acting β_1 blocker esmolol. It may also be used along with a loop diuretic in selected cases of acute hypertensive heart failure.

Due to its potency and rapidity of action, nitroprusside needs a precise infusion pump and intra-arterial BP monitoring. Nitroprusside generates cyanide and thiocyanate which can produce CNS and other toxicities. In ischaemic stroke, it may further compromise cerebral blood flow, while intracranial pressure may be further raised in haemorrhagic stroke. Nitroprusside is better avoided in these conditions.

6. Furosemide (20–80 mg slow i.v.) This high ceiling diuretic (*see* Ch. 41) is not a hypotensive, but may be given as a useful adjunct with any of the above drugs, particularly vasodilators, if there is volume overload (in acute LVF, pulmonary edema) or cerebral edema (in encephalopathy). It needs to be avoided when patient may be hypovolemic due to pressure induced natriuresis (especially in eclampsia, pheochromocytoma).

7. Hydralazine Injected i.m. or i.v. slowly, hydralazine (*see* p. 627) acts in 20–30 min, and keeps BP low for 4–6 hours, but is less predictable. It is an alternative drug that has been used for preeclampsia and eclampsia. It causes reflex tachycardia, and must be given along with a β blocker, and should be avoided in patients with myocardial ischaemia or aortic dissection.

Fenoldopam (dopamine agonist), *Clevidipine* (ultrashort acting DHP) and *enalaprilat* (a parenteral ACE inhibitor) are the other drugs that are used in hypertensive emergencies, but are not available in India.

Oral drugs

Oral hypotensive drugs that lower BP over a period of 2–48 hours may be more appropriate and safer in hypertensive urgencies, when there is no immediate threat to life or of organ damage. The following oral drugs have been used:

1. Labetalol In a dose of 100–200 mg BD, it is a moderately potent hypotensive (*see* p. 181), that starts acting after 2–4 hours and is satisfactory in many cases of severe hypertension without TOD. Labetalol is particularly suitable in preeclampsia, pheochromocytoma, stroke and ischaemic heart disease, but is contraindicated in the presence of heart failure.

2. Amlodipine This slow and long acting DHP (*see* p. 610) has been effectively and safely employed in many cases of severe hypertension, when raised BP is the only finding and there is no impending TOD or threat to life. In a dose of 10 mg oral repeated after 12 hours and then once daily, it starts acting in 6–8 hours and may take 2–4 days to lower BP to target level. It is particularly suitable for elderly patients and those prone to postural hypotension.

3. Clonidine (see p. 626) Oral clonidine (100 µg every 1–2 hours) lowers BP within a few hours, but produces sedation, dry mouth and rebound rise in BP on stopping. It is not suitable for the elderly, and is seldom used.

4. Captopril This non-prodrug, rapidly acting ACE inhibitor (*see* p. 562), has also been used orally (25 mg repeated as required) in hypertensive urgencies. Though it may lower BP in 30 min, the response is unpredictable both in intensity as well as in latency. It is not favoured now.

Oral or sublingual use of *immediate release nifedipine* capsules in hypertensive urgencies has been abandoned because of unpredictable intensity of action.

PROBLEM DIRECTED STUDY

40.1 A 70-year-old male of Indian origin presented with complaint of dull headache, giddiness, weakness and occasional breathlessness. He gave history of left sided paralytic stroke about 2 years back, from which he has recovered nearly completely, and is taking Aspirin 75 mg per day. The pulse was 66/min. The BP was found to range between 152–160 mm Hg systolic and 82–86 mm Hg diastolic, when measured on 3 occasions over one week. The ECG showed signs of left ventricular hypertrophy, but no ischaemia. Fundus examination revealed mild age related changes. Fasting blood sugar was 96 mg/dl; kidney function, liver function tests and lipid profile were within normal range.

(a) Should he be prescribed antihypertensive medication? If so, whether one, or more than one, antihypertensive should be prescribed concurrently, and which drug/drugs will be more suitable for him?

(*see* Appendix-1 for solution)

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