

Chapter 41 | Antihypertensive Drugs

These 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 cutoff manometric reading between normotensives and hypertensives is arbitrary. For practical purposes 'hypertension' could be that level of BP at or above which long-term antihypertensive treatment will reduce cardiovascular mortality. Almost all HT management guidelines including NICE (2011), JNC8 (2014), WHO-ISH (2003), European Society of Hypertension (2007, 2013) 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.

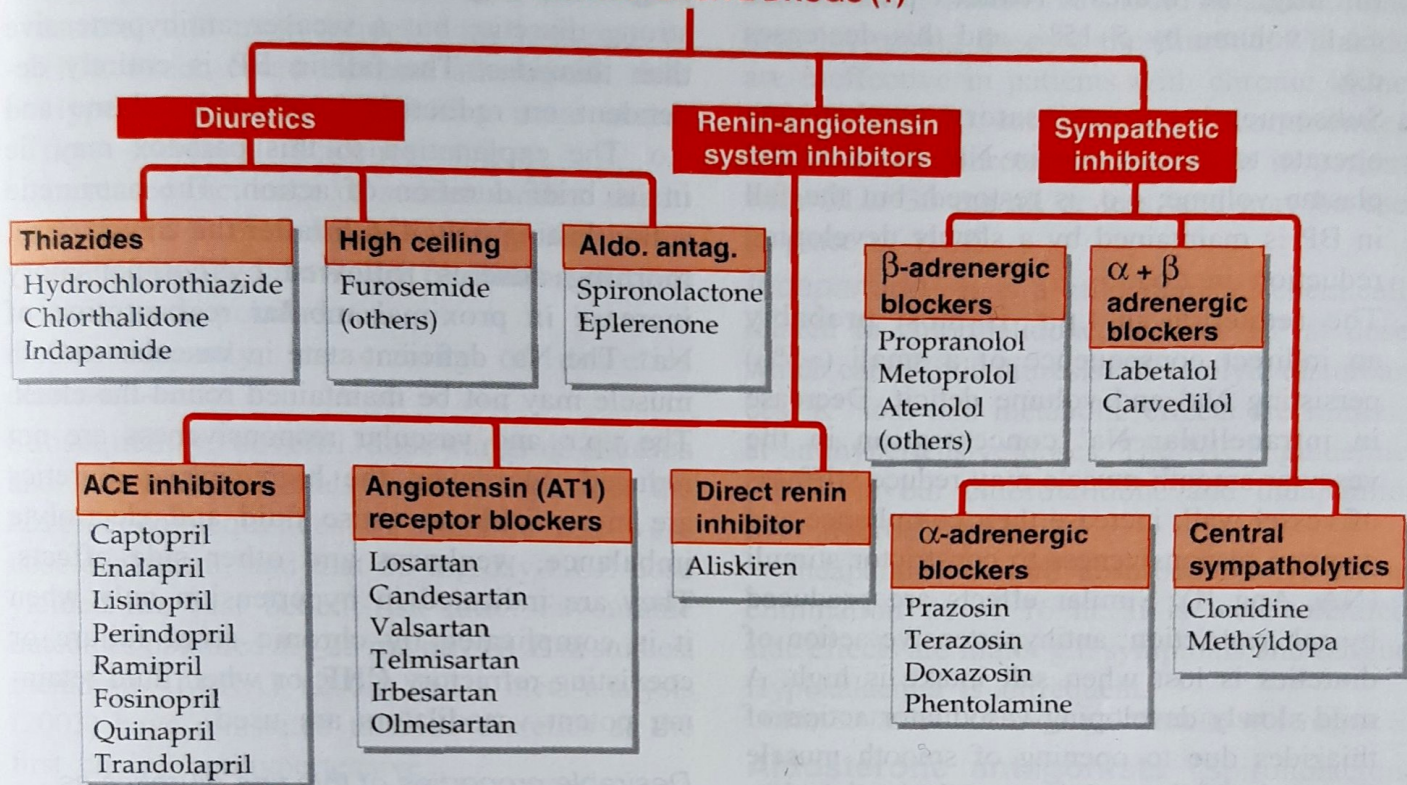
Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and renin-angiotensin systems (RAS) may or may not be overactive, but they do contribute to the tone of blood vessels and c.o. in hypertensives, as they do in normotensives. Many antihypertensive drugs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

regulatory systems at one level or the other. Antihypertensive drugs, by chronically lowering BP, may reset the barostat to function at a lower level of BP.

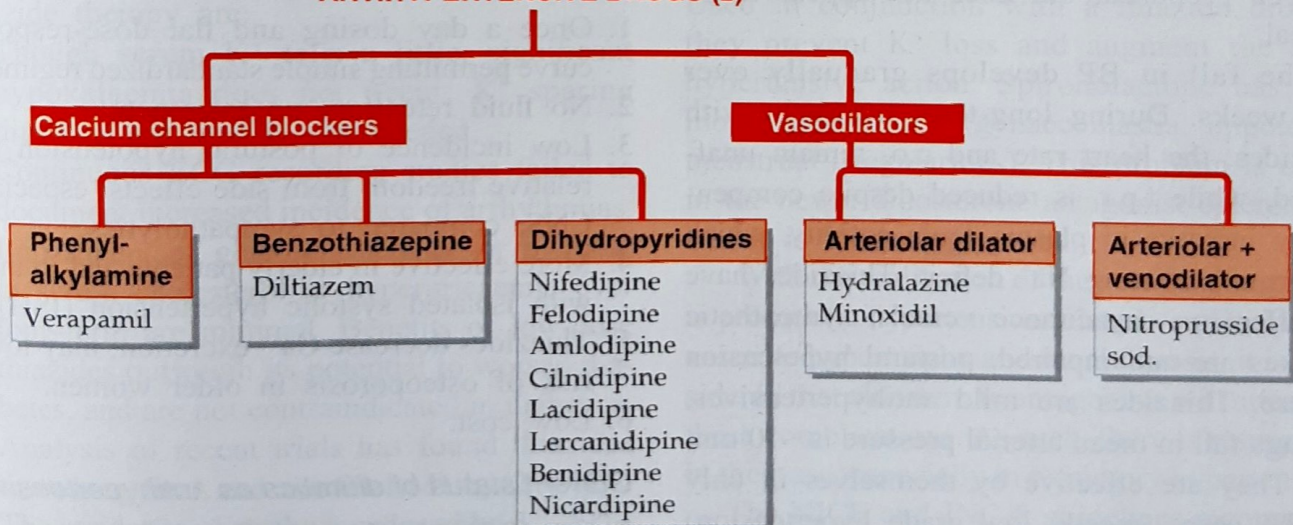
Antihypertensive drug therapy has been remarkably improved in the last 60 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive was available. *Veratrum* and *Sod. thiocyanate* could lower BP, but 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. *Guanethidine* introduced in 1961 was an improvement on ganglion blockers. The antihypertensives of the 1960–70s were *methyldopa*, β blockers, *thiazide* and *high ceiling diuretics* and *clonidine*. 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 (*losartan*, etc.) were added soon after, and the direct renin inhibitor *aliskiren* is the latest drug. 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.

- JNC 7—The seventh report of Joint National Committee (of USA) on prevention, detection, evaluation and treatment of high blood pressure.
- JNC 8—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)).
- NICE (2011)—National Institute for Health and Care Excellence (UK); Hypertension in adults: diagnosis and management (CG127).
- WHO-ISH—World Health Organization and International Society of Hypertension.

ANTIHYPERTENSIVE DRUGS (1)



ANTIHYPERTENSIVE DRUGS (2)



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. 42.

Thiazides Hydrochlorothiazide (HCZ) and chlorthalidone are the diuretic of choice for uncomplicated hypertension; have similar efficacy and are dose to dose equivalent. All

megatrials 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; favoured 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 this decreases c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na^+ balance and plasma volume; c.o. is 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). Similar effects are produced by salt restriction; antihypertensive action of diuretics is lost when salt intake is high. A mild slowly developing vasodilator action of thiazides due to opening of smooth muscle K^+_{ATP} channels and hyperpolarization has been proposed, but does not appear to be real.

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. Thiazides have no effect on capacitance vessels, sympathetic reflexes are not impaired: postural hypotension is rare. Thiazides are mild antihypertensives, average fall in mean arterial pressure is ~10 mm Hg. They are effective by themselves in only ~30% cases (mostly low grade hypertension) 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 any grade of hypertension. They 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. Low incidence of postural hypotension and relative freedom from side effects, especially CNS, compared to sympatholytics.
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 inhibition of insulin release (probably secondary to K^+ depletion).

- 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 decreased.

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 the first choice antihypertensive.

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

- Though serum K^+ falls a little, 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, and are not contraindicated in diabetics.
- Analysis of recent 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 recent trials in mild to moderate hypertension have found thiazides to reduce left ventricular hypertrophy.

The JNC 8, NICE (2011) and other guidelines recommend instituting 12.5–25 mg/day thiazide therapy, with or without added K^+ sparing diuretic, as a first choice treatment of essential hypertension, especially in the elderly. 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; reduces BP at doses which cause little diuresis. Electrolyte disturbances, K^+ loss and metabolic effects are minimal at antihypertensive doses. The NICE guidelines (2011) favour chlorthalidone and indapamide over hydrochlorthiazide.

Indapamide is well absorbed orally, has an elimination $t_{1/2}$ 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, 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 regimen, if the target level BP is not attained. 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 diuretic/ β blocker extends efficacy to ~90%. 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 appear to be 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 on p. 535–37. In a dose of 50 mg/day losartan 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 (2011) 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 the only available member of the latest class of RAS inhibitors which act by blocking catalytic activity of renin and inhibiting production of AngI and AngII. 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. 40. All 3 subgroups of CCBs, viz. dihydropyridines (DHPs, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives, but DHPs are mainly used. They lower BP by decreasing peripheral resistance without compromising c.o. Despite vasodilatation, fluid retention is insignificant.

Ankle edema that occurs in some patients 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 ~ 60% hypertensives, and they may improve arterial compliance. 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 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; can be used during pregnancy (but can weaken uterine contractions during labour).

The initial large controlled trials (HINT, TRENT, SPRINT I, II) and metaanalysis has consistently indicated increased mortality/reinfarction in patients treated with standard nifedipine (or other short-acting DHP) formulations. The increased mortality among coronary heart disease patients has been attributed to repeated surges of adrenergic discharge and marked swings of BP attending each dose of rapidly acting DHP. However, this risk cannot be extrapolated to verapamil/diltiazem as brought out by DAVIT I, II and other controlled studies, as well as to slow acting DHPs (amlodipine type).

The Systolic hypertension in Europe (Syst-EUR) trial has shown that nitrendipine (long-acting DHP) reduces cardiovascular morbidity and mortality in elderly hypertensives. The Hypertension optimal treatment (HOT), and Swedish trial in old patients with hypertension-2 (STOP-2) studies have also found CCBs equi-effective as diuretics/ β blockers/ACE inhibitors in reducing major cardiovascular events as well as cardiovascular/total mortality. No excess mortality with the use of amlodipine in post MI and acute coronary syndrome patients has been noted in the ALLHAT (2002) study. On the other hand, CCBs do not afford survival benefit in post MI patients as β blockers, ACE inhibitors or low dose thiazides do. CCBs are also not as effective in suppressing left ventricular hypertrophy (a major risk factor in ischaemic heart disease) as ACE inhibitors.

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-2011 guidelines) because of their high efficacy and excellent tolerability. Also 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. However, the negative inotropic and dromotropic action of verapamil and diltiazem may worsen CHF and cardiac conduction defects, but DHPs are safe.

β -ADRENERGIC BLOCKERS

The pharmacology and mechanism of antihypertensive action of β blockers is described in Ch. 10. They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40% patients—mostly stage I cases. Additional BP lowering may be obtained when combined with other drugs.

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. Drugs with intrinsic sympathomimetic activity (ISA) cause less/no reduction of HR and c.o. but decrease vascular resistance by β_2 agonism. 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 preferred by many experts on theoretical grounds.

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 (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, but all-cause mortality has been decreased in long-term trials. Hypertensives with stable heart failure should be treated with one of the selected β blockers (metoprolol/bisoprolol/carvedilol/nebivolol) along with an ACE inhibitor/ARB (CIBIS, 1999; MERIT-HF, 1999, COPENICUS, 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 older hypertensive. 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 appear to 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 (JNC 8, NICE guidelines 2011).

$\beta + \alpha$ ADRENERGIC BLOCKERS

Labetalol (see Ch. 10). 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. 619). 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 $\beta +$ 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. 10)

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 (pre-synaptic) receptors are not blocked: autoregulation of NA release remains intact. Prazosin probably decreases central sympathetic tone as well.

Renal blood flow and g.f.r. are maintained but fluid retention may attend fall in B.P. 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 $t_{1/2}$ 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.; **PRAZO-PRESS** 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 a diuretic + β blocker in those not achieving target BP.

Terazosin, Doxazosin These are long-acting congeners of prazosin with similar properties but suitable for once daily dosing (see p. 155–56). In the ALLHAT (2002) study doxazosin monotherapy has doubled the incidence of CHF; but this can occur with any α_1 blocker. A higher incidence of stroke relative to patients receiving a thiazide diuretic was also noted.

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. They block both α_1 and α_2 receptors—NA release is accentuated. 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 mainly postjunctionally in medulla (vasomotor centre). This decreases sympathetic out flow resulting in fall in BP and bradycardia. Enhanced vagal tone contributes to 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 $t_{1/2}$ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

Dose: Start with 100 μ g OD or BD, max. 300 μ g TDS, orally or i.m.

CATAPRES 150 μ g tab, **ARKAMIN** 100 μ g 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 choice drug. There is no data on prognostic benefits, if any, of clonidine. At present, it is occasionally used in combination with a diuretic.

Other indications

1. Opioid withdrawal: Opioid and α_2 adrenergic systems converge on the same effectors in many systems; both activate the G_i 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.

4. Clonidine has been used to control loose motions due to diabetic neuropathy. It may be acting by α_2 receptor mediated enhancement of salt absorption in gut mucosa.

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 or c.o. In large doses, methyldopa inhibits the enzyme dopa decarboxylase. It was initially believed that methyldopa acted as antihypertensive by depressing synthesis of NA in peripheral sympathetic neurones, and by generating α methyl NA which acted as a *false* (weak) *transmitter*. Subsequently α methyl NA was found to be as potent vasoconstrictor as NA. Many other findings have later confirmed the primary central site of action of methyldopa.

Methyldopa is a moderate efficacy anti-hypertensive. Circulating levels of NA and renin tend to fall 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, 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 anti-hypertensive 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 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 $\rightarrow$ increased aldosterone $\rightarrow$ 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 may occur 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 block 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, $t_{1/2}$ 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 only in combination with a diuretic and/or β blocker for patients not achieving target BP with first line drugs. It is one of the antihypertensives that has been 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 employed in the management of CHF particularly in combination with isosorbide dinitrate (see p. 566).

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. 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 therapy is discontinued. The mechanism of increased hair growth is not known; may involve:

- (a) Opening of K^+ channels and enhanced 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 relaxes 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 (also see p. 544). This occurs both enzymatically and nonenzymatically. The enzymes involved are different from those that produce NO from glyceryl trinitrate. Nonenzymatically it is converted to NO (and CN) 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. 619). 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. It decomposes at alkaline pH and on exposure to light: the infusion bottle should be covered with black paper.

Nitroprusside is split to release cyanide. The latter is converted in 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. 566) and in acute mitral regurgitation.

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

ADRENERGIC NEURONE BLOCKERS

Reserpine It is an alkaloid from the roots of *Rauwolfia serpentina* (sarpagandha) indigenous to India which has been used in 'Ayurvedic' medicine for centuries. The pure alkaloid was isolated in 1955 and later found to act by causing CA and 5-HT depletion. It was a popular antihypertensive of the late 1950s and early 1960s, but is now used only as a pharmacological tool.

Reserpine acts at the membrane of intraneuronal vesicles which store monoamines (NA, DA, 5-HT) and irreversibly inhibits the vesicular monoamine transporter (VMAT2). The monoamines are gradually depleted and degraded by MAO. The effects last long after the drug is eliminated (hit and run drug) because tissue CA stores are restored only gradually.

Higher doses deplete CAs and 5-HT in the brain as well; cause sedation and mental depression. Antipsychotic effect (mild) and extrapyramidal symptoms are produced due to DA depletion.

Guanethidine It is a polar guanidine compound which is taken up into the adrenergic nerve endings by active amine transport, where it inhibits nerve impulse-coupled release of NA.

Guanethidine has gone out of use now due to marked side effects.

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 (2011) have graded hypertension as:

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

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 JNC7 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 compelling indications may suggest fixing a lower target BP value to be attained by drug therapy.

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

Beneficial effects 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 compelling indications 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 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

(life style 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.

Selection of antihypertensive drug/combination

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) 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. 610.

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 (if present); but for the majority of hypertensive patients who have no compelling indication, *age* and *race* has been recognized as valid basis for selecting the initial medication. Because 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

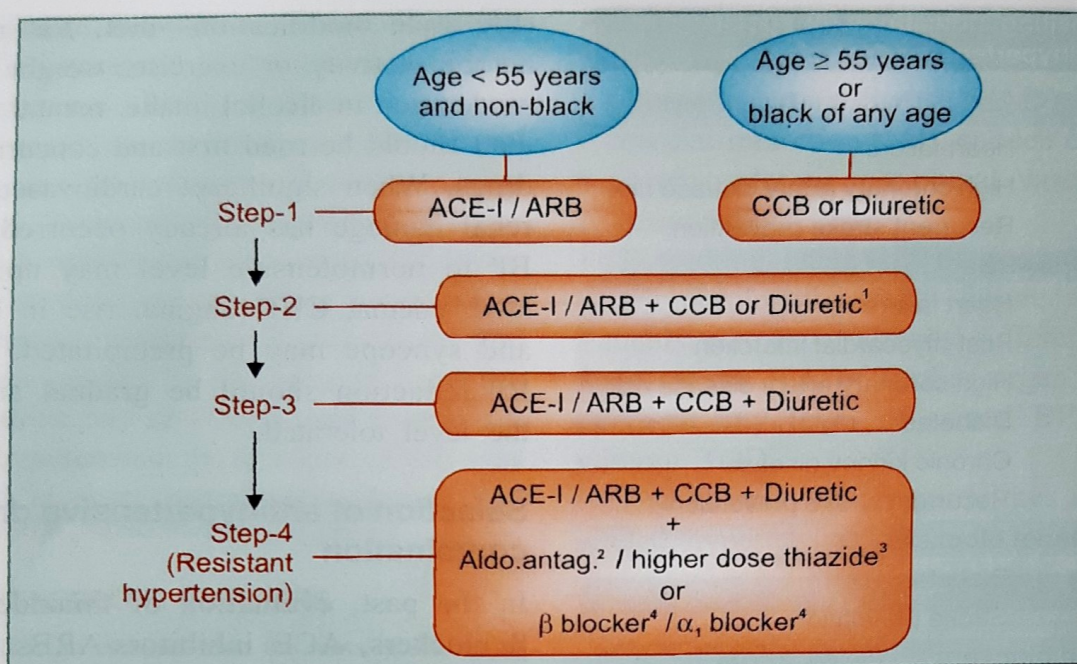


Fig. 41.1: Schematic depiction of stepwise drug treatment guideline for hypertension recommended by National Institute for Health and Care Excellence (UK) 2011

1. A thiazide diuretic to be considered only if calcium channel blocker (CCB) cannot be used, e.g. patient has edema/heart failure/high risk of heart failure.
2. Aldosterone antagonist (Aldo. antag.) to be used only when serum K^+ is <4.5 mmol/L.
3. Higher dose of thiazide to be used only when serum K^+ is >4.5 mmol/L.
4. β blocker or α_1 blocker to be considered only if aldosterone antagonist or higher dose thiazide is ineffective or not tolerated or contraindicated.

ACE-I—Angiotensin converting enzyme inhibitor, ARB—Angiotensin receptor blocker.
<https://www.nice.org.uk/guidance/cg127> (last updated Nov 2016).

or CCB. 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 (see Fig. 41.1). 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, 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 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 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 higher dose of the thiazide (if serum K^+ is >4.5 mmol/L) or a β blocker (especially β blocker with vasodilating property, viz. carvedilol, nebivolol) or a selective α_1 blocker.

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. ACE inhibitor with an ARB.
4. Verapamil or diltiazem with β blocker, because marked bradycardia, A-V block can occur.
5. Methyldopa with clonidine or any two drugs of the same class.
6. 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-HT**
9. Losartan 50 mg + Ramipril 2.5 mg or 5 mg—**TOZAAR-R, LAPIDO-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 toxemia of pregnancy—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 80–100 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 toxemia 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.

Diuretics: There is some evidence that by reducing blood volume, diuretics tend to accentuate uteroplacental perfusion deficit (of toxemia)—increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.

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 $\alpha + \beta$ adrenergic blocker (see p. 165) given orally is effective in majority of cases, and is most widely used now.

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 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 TOD determines the seriousness of the condition.

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).
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, 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, nitro dilators) and adrenergic blockers meet these requirements best.

1. Nicardipine This is one of the few DHPs available for parenteral (i.v.) use, and has lately 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 $t_{1/2}$ 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. Sodium nitroprusside (see p. 613) 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 restricted its use. The major indication now is 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.

3. Glyceryl trinitrate (GTN) Infused i.v. (5–20 $\mu\text{g}/\text{min}$) 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 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.

4. Labetalol Unlike pure β blockers, this combined β and α adrenergic blocker is an efficacious hypotensive when injected i.v. (see p. 165), 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.

5. Esmolol This short acting selective β_1 blocker (see p.163) given as 0.5 mg/kg bolus i.v. injection followed by 50–200 $\mu\text{g}/\text{kg}/\text{min}$ 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 or nitroprusside 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.

6. Phentolamine This non-selective $\alpha_1 + \alpha_2$ adrenergic blocker (see p.155) is an alternative drug to labetalol for hyperadrenergic states, e.g. hypertensive episodes in pheochromocytoma. Injected i.v. (5–10 mg) it acts in 2 min and action lasts 5–15 min. Tachycardia and myocardial ischaemia may complicate its use, for which a β blocker may be added.

7. Hydralazine Injected i.m. or i.v. slowly, hydralazine (see p. 612–13) 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 particularly used for preeclampsia/eclampsia. It causes tachycardia, and should be avoided in patients with myocardial ischaemia or aortic dissection. A β blocker may be combined.

8. Furosemide (20–80 mg slow i.v.) This high ceiling diuretic (*see* Ch. 42) 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).

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.165), 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.595) 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. Captopril This non-prodrug, rapidly acting ACE inhibitor (*see* p. 530–31), 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.

4. Clonidine (*see* p. 611) 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 seldom used.

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

PROBLEM DIRECTED STUDY

41.1 A 70-year-old male 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, but 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)