

HYPERTENSION IN SPECIAL SITUATIONS

Hypertension with diabetes mellitus

- Co-existence of hypertension and diabetes is being increasingly recognised. 30-35% of hypertensives are detected to have diabetes.
- The prevalence of hypertension is 1.5 to 2 times greater in patients with diabetes mellitus compared with matched non-diabetic individuals.⁹⁰
- In India, it is predicted that there is going to be a steep increase in the number of Type II diabetic patients.⁹¹
- Coexistence of diabetes and hypertension increases the risk of macro and microvascular disease.
- Blood pressure should be measured in the supine, sitting and standing positions in a diabetic patient to detect evidence of autonomic neuropathy.
- UKPDS has stressed the importance of effective blood pressure control irrespective of the antihypertensive agent used.³⁰ The study also shows that polypharmacy, i.e. use of two or more drugs is required for optimal control. The HOT study in diabetic patients has shown significantly lower risk of cardiovascular disease in those patients assigned to the lowest target blood pressure (<130/85 mm Hg).²⁹
- In the management of diabetic hypertensives, lifestyle modifications have to be more aggressive.
- Pharmacological treatment of hypertension in diabetic patients differs due to effects of certain drugs on the lipid profile, insulin sensitivity and glucose metabolism.
- ACE inhibitors⁹² have been shown to slow the rate of decline in renal function in diabetic patients. The Heart Outcomes Prevention Evaluation Study (HOPE) emphasized the importance of ACE inhibitors to reduce the risk of complications of diabetes.⁶¹ ACE inhibitors are recommended as first line drugs for management of diabetic hypertensives.
- Beta-blockers potentially mask hypoglycemic symptoms, however at present it is not a major contraindication. Further, there is clear evidence of benefits of beta-blockers in diabetic patients after myocardial infarction.³⁰
- CCBs may be useful in diabetes, alone or in combination to control BP. In ASCOT trial, combination of amlodipine and perindopril was associated with significantly less incidence of new onset diabetes than combination of beta blocker and diuretic.³⁹
- Alpha-blockers are metabolically beneficial in hypertensive diabetic patients.
- Tight metabolic control of diabetes, effective blood pressure control and low protein diet improves overall outcome.

Hypertension with renal disease

- Hypertension results from any form of renal disease that reduces the number of functioning nephrons leading to sodium and water retention.⁹³ Hypertension is widely prevalent in all forms of renal diseases.
- Hypertension is more common in glomerular than in tubulointerstitial disease and chronic pyelonephritis. Microalbuminuria may be a marker of generalized endothelial dysfunction.
- Reducing BP to <125/75 mm Hg may produce additional benefit in patients with chronic renal disease of any aetiology associated with proteinuria of ≥ 1 g per 24 hours. It is emphasised, however, that this concept that 'lower is better' for patients with renal disease and hypertension is based on limited evidence, and is largely extrapolated from retrospective analysis of clinical trial data.⁹

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- In end stage renal disease of any cause (except diabetes), hypertension is present in more than 75% of the cases.
- It is now documented that all patients with microalbuminuria, irrespective of presence or absence of hypertension, need to be treated with antihypertensive drugs which retard the progression of renal failure.^{94,95}
- Sodium (<4 g/day) and protein restriction (0.6 g/kg/day) form an integral part of the dietary treatment.
- One should be cautious in the use of ACE inhibitors in patients with persistent rising levels of serum potassium and creatinine.
- Low dose diuretics, calcium channel blockers, alpha-blockers, beta-blockers and alpha methyldopa can all be used in these patients.
- Dialysis may control blood pressure due to regulation of fluid volume and electrolytes. However, drug therapy is required in 80-90% of the patients.
- Most patients will require 3 or more drugs to achieve the recommended blood pressure (BP) goal. For patients with chronic kidney disease, ACE inhibitors and ARBs have demonstrated favorable effects on progression of diabetic and non-diabetic renal disease.² As ACE inhibitors and ARBs are increasingly being recommended for the management of hypertension, a note of caution is warranted: Chronic renal failure as opposed to chronic renal disease is a condition where they can have a deleterious effect on GFR and serum creatinine and potassium levels have to be monitored carefully. Diuretics are effective in achieving blood-pressure control in patients with hypertension. The use of low-dose thiazide diuretics in combination with ACE inhibitors usually does not lead to changes in renal function. CCBs exert a vasodilatory effect on the afferent arteriole and are therefore less likely to cause a reduction in the glomerular filtration rate when the blood pressure is lowered. Non-dihydropyridine CCBs are consistently associated with a beneficial effect on renal function; such benefit may be additive when these drugs are combined with an ACE inhibitor. If a dihydropyridine CCB is to be given to patients with established nephropathy, it should be given with either an ACE inhibitor or an angiotensin-receptor blocker.⁹⁶ CCBs represent an important, well-tolerated therapeutic option for those who cannot tolerate ACE inhibitors/ARBs, or when concomitant therapy is required for adequate BP control.⁹⁷ Beta-blockers are effective agents for the treatment of hypertension in both diabetic and nondiabetic chronic renal disease. In general, these drugs have no clinically important effects on renal hemodynamics and the glomerular filtration rate.⁹⁶ The National Kidney Foundation states that alpha-blockers may be a useful adjunct to the control of blood pressure, but have not been shown to have a unique cardio or renoprotective benefit in this patient population. Alpha-blockers are effective in lowering blood pressure and are associated with favorable metabolic profiles in patients with diabetes. However, these agents have not been shown to reduce either albuminuria or CV mortality in people who develop heart failure.^{9,98}

Hypertension with cerebrovascular disease

- The evidence for reduction in incidence of stroke with control of blood pressure has been consistent. In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35% to 40%.^{2,31}
- Immediately after the occurrence of an ischemic cerebral infarction, it is appropriate to withhold treatment in patients who present with high blood pressure, unless blood pressure is very high (>200/120 mm Hg).
- In stroke survivors with hypertension, blood pressure lowering therapy has been shown to result in 43% reduction in stroke recurrence.⁹⁹
- Extensive elevation of blood pressure with slow elevation is more often associated with cerebral haemorrhage than infarction. Moderate reduction in blood pressure is prognostically more rewarding in haemorrhagic stroke than in ischemic stroke.¹³

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- In clinically evident cerebrovascular disease, the goal is to gradually reduce the blood pressure and carefully monitor it for the first 24 hours in view of the possibility of transient hypertension.
- Hypertensive encephalopathy is an emergency that needs to be identified and aggressively managed.
- BP should not be reduced in ischemic stroke patients who are otherwise not candidates for thrombolysis. In patients for thrombolytic therapy, SBP \geq 185 and DBP \geq 110 mm Hg should be actively treated and maintained below 185/110 mm Hg.¹⁰⁰
- In acute intracerebral hemorrhage, the SBP and DBP should be maintained below 180/105 mm Hg respectively.¹⁰⁰

Hypertension in women

- Some of the side effects of commonly used drugs like ACE inhibitor induced cough, CCB induced pedal edema, and diuretic induced hyponatremia and hypokalemia are seen more often in women than in males.^{2,101}
- Estrogen-progesterone oral contraceptives cause a distinct increase in systolic and to a lesser extent diastolic pressure in virtually all women. Five percent women who use the pill for 5 years develop hypertension. Age, positive family history, history of PIH and obesity are known predisposing factors for pill-induced hypertension.^{2,102} In more than one half, blood pressure returns to normal when the pill is withdrawn.
- The use of hormone replacement therapy in post-menopausal women (low dose estrogen) is not contraindicated in women with hypertension.

Hypertension in pregnancy

- Hypertension occurs in about 5% of all pregnancies. In developed as well as developing countries, hypertensive disorder of pregnancy is one of the leading causes of maternal and perinatal mortality.^{103,104}
- Hypertension in pregnancy is diagnosed by recording phase IV of Korotkoff sounds with the patient lying in a lateral position. DBP $>$ 85 mm Hg should be considered abnormal. The diagnosis requires two consecutive measurements of DBP of 90 mm Hg or more.
- Diastolic blood pressure \geq 110 mm Hg is considered ominous and requires urgent attention.
- If this disorder is diagnosed early and managed appropriately, morbidity and mortality can be largely prevented.
- Chronic hypertension is that which is present before pregnancy or is diagnosed before 20th week of gestation or that which persists beyond six weeks post partum.
- Pre-eclampsia is a pregnancy specific condition characterized by increased blood pressure appearing after 20 weeks of gestation and usually accompanied by oedema and proteinuria. Eclampsia is the occurrence of seizures that cannot be attributed to other causes in a patient with pre-eclampsia.
- Pre-eclampsia superimposed on chronic hypertension is diagnosed when there is a further increase in BP of 30 mm Hg systolic or 15 mm Hg diastolic together with the appearance of proteinuria or oedema.
- Transient hypertension is elevation of BP during pregnancy or during first 24 hrs post partum with no other signs of pre-eclampsia or of pre-existing hypertension.
- Benefits of low-dose aspirin prophylaxis are unproven for most women, including nulliparous women.¹⁰⁵

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- The antihypertensive agent used should be efficacious and safe to the mother and the foetus. Methylodopa has been evaluated most extensively and is therefore recommended for women whose hypertension is first diagnosed during pregnancy. Calcium channel blockers, beta-blockers, in particular, pindolol, oxprenolol, and labetalol can be used. Drugs like atenolol have been shown to cause foetal retardation. Alpha-blockers may also be used.^{106,107}
- ACE inhibitors and angiotensin II receptor blockers are contraindicated in pregnancy. Use of low dose diuretics is discouraged, since pre-eclampsia is a volume-depleted state.¹⁰⁸
- Intravenous magnesium sulphate is the drug of choice both for prevention and treatment of seizures.^{109,110} Intravenous hydralazine and labetalol are effective agents, but are not currently available in India.
- In some cases, antihypertensive treatment fails to control hypertension and the only means of controlling hypertension would be to induce delivery.

Hypertension in the elderly

The prevalence of hypertension increases with age. The population of India aged 65 years and above is projected to increase from 51 million in 2005 to 65 million in 2015 and 76 million in 2020.¹¹¹ The prevalence of hypertension is age related, being the highest in the age group of 50-59 years in males and 60-64 years in females in urban areas. In rural areas, an age related increase is seen in both the sexes in the age group of 60-64 years. A community based study in Mumbai¹¹² in 1980 showed increase in BP with age, with prevalence in 15% of total population surveyed, 34.5% in those over 55 years, 38.5% in those over 65 years and 44.4% in those over 70 years.

In elderly population, systolic blood pressure is a better predictor of cardio-vascular/cerebrovascular events, end-stage renal disease and all-cause mortality, as compared to diastolic blood pressure.¹¹³

Precautions in measurement

Blood pressure should be measured with care in elderly subjects as some older patients may have falsely high readings due to excessive vascular stiffness. Also as older patients are more likely to have orthostatic hypotension, one should measure BP in supine, sitting and standing positions.

Treatment of hypertension in elderly nowadays is accepted as a highly effective medical intervention. An overview of five randomised trials have shown 34% reduction in stroke, 19% in CHD and 23% in vascular deaths, with a reduction of 12-14 mm Hg SBP and 5-6 mm Hg DBP over a five year period.¹¹⁴

Management

- Lifestyle modification is important in management of hypertension in elderly and should be started in all of these patients. Losing weight and cutting down on salt can lessen and even eliminate the need for blood pressure lowering medications in elderly (Trial of Non-pharmacological Interventions in the Elderly - TONE).¹¹⁵
- Drug treatment: The blood pressure should be lowered gradually in elderly hypertensives with no more than an initial 25% decrease, even in situations requiring rapid reduction in blood pressure with medications.
- Low dose thiazide diuretics are recommended, because they have been shown to be effective in reducing mortality and morbidity. Unless there is a compelling indication to use another class of drugs, low dose hydrochlorothiazide or chlorthalidone 12.5 to 25 mg per day should be the first choice. This could also be combined with potassium sparing diuretic like amiloride 2.5 mg or triamterene 50 mg per day. Long-acting dihydropyridine CCBs such as nitrendipine and amlodipine

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are considered to be appropriate alternatives in these patients. Depending on the associated conditions, beta-blockers, ACE inhibitors, or alpha-blockers may be the preferred drugs in special situations. Alpha-blockers are the preferred drugs in presence of BPH. In STOP 2, there was some evidence that the risk of myocardial infarction and of heart failure were greater with calcium antagonist based therapy than with ACE inhibitor based therapy. There were no clear differences between either of these regimens and a third based on diuretics and beta-blockers.¹¹⁶

- Bilateral atherosclerotic renovascular disease in the elderly must be kept in mind while treatment with ACE inhibitors or ARBs.

Isolated systolic hypertension

Isolated systolic HT is more often seen in the elderly than in the young. The goal of blood pressure control in older patients should be the same as in younger patients (i.e., 140/90 mm Hg)³; however an interim value of a systolic blood pressure below 160 mm Hg may be necessary in elderly patients with marked systolic hypertension, especially if they develop symptoms of giddiness and light headedness when their blood pressure is reduced to 140/90 mm Hg. Management of isolated systolic hypertension in the elderly is the same as mentioned in the management of hypertension in the elderly.

Isolated systolic hypertension in the young patients, although uncommon, is often successfully treated with life style modification and long-acting beta-blockers.

Hypertension with congestive cardiac failure

Congestive cardiac failure is a common sequel of long standing hypertension and adequate control of BP improves mortality in these patients.

- Several large trials of ACE inhibitors in patients with left ventricular dysfunction due to hypertension, have provided evidence of significant reduction of morbidity, secondary to heart failure.¹¹⁷
- Low dose diuretics are also used in hypertension with heart failure, particularly when associated with fluid retention.
- In patients with congestive heart failure stabilized with ACE inhibitors and diuretics, selective beta-blockers such as metoprolol, bisoprolol and alpha-beta blocker carvedilol may be used wherever indicated. Use of these beta-blockers has been shown to reduce mortality. These agents should be started in low doses and then gradually increased.¹¹⁸⁻¹²⁵
- Amlodipine has been found to be safe in treating hypertensive patients with angina and left ventricular failure, when added to ACE inhibitors, low dose diuretics and digoxin.⁶⁰ Other calcium channel blockers are not recommended in these patients.³
- In patients with severe hypertension and acute left ventricular failure, blood pressure needs to be brought down rapidly to normal or slightly above normal range. This can be done by administration of intravenous drugs such as furosemide, nitroglycerine, enalaprilat or sodium nitroprusside.

Hypertension with chronic obstructive airway disease

- Hypertension in patients with COAD and bronchial asthma is seen. It is often precipitated by the use of systemic steroids, beta-agonists or nasal decongestants. Stress also plays a significant role in the development of hypertension in these patients. It is therefore recommended that the above precipitating factors should be looked for and modified.
- Long acting calcium channel blockers such as amlodipine have been found to be relatively safe drugs in this group of patients.³
- ACE inhibitors have not been found to increase bronchial reactivity in these patients. It is

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recommended that if cough develops, angiotensin II receptor blockers should be tried as alternative to ACE inhibitors.

- Beta-blockers and alpha-beta blockers are not recommended as they are known to exacerbate asthma. However, alpha-blockers can be used in patients with COAD.¹²⁶
- Inhaled corticosteroids and ipratropium bromide can be used safely in these patients.

Hypertension with coronary artery disease (CAD)

Among all the risk factors documented for pathogenesis of CAD, hypertension is reported to be the major risk factor.¹²³ Blood pressure levels have been shown to be positively and continuously related to the risk of major CAD events.⁸²

- Too rapid lowering of blood pressure, which can cause reflex tachycardia and sympathetic activation, should be avoided in patients with CAD.
- One may have to set the target of BP control even below 130-140/90 mm Hg.
- All other risk factors should be treated appropriately.
- HT in patients with acute coronary syndrome should be treated aggressively.
- Beta-blockers and CCBs are the drugs of first choice in the management of angina in patients with hypertension associated with CAD.
- Beta-blockers have been shown to reduce the risks of re-infarction and cardiovascular death by 25% in patients with MI.¹²⁷
- Amlodipine has been shown to produce subjective and objective improvement in patients with angina.¹²⁸
- Treatment with amlodipine is associated with fewer hospitalisations for unstable angina and revascularisations in patients with angiographically documented CAD.¹²⁹
- Verapamil and diltiazem reduce risk of developing MI following non-Q-wave myocardial infarction.¹³⁰
- After MI, therapy with ACE inhibitors prevents subsequent heart failure and reduces morbidity and mortality.¹³¹ ACE inhibitors in combination with digoxin or low dose diuretics, are effective in reducing morbidity and mortality in patients in heart failure.¹³²
- Statins and aspirin are recommended in patients with hypertension associated with CAD.

Hypertension with dyslipidaemia

Dyslipidaemia often co-exists with hypertension.¹³³

- Lifestyle modification is of particular importance in such patients as it can lower blood pressure and improve lipid levels.
- The choice of antihypertensive agent should be made after considering the effects on the lipid profile that some of these drugs have.
- In high doses, low dose diuretics can induce at least a short-term increase in cholesterol, triglycerides and LDL cholesterol levels. Low dose thiazides do not produce this effect. In spite of these effects on the lipid profile, these drugs when used as monotherapy or in combination, reduce mortality due to CAD and cerebrovascular disease.
- Beta-blockers without intrinsic sympathomimetic activity (ISA) may increase levels of plasma triglycerides and reduce levels of HDL-cholesterol. Despite this, these have been shown to reduce rate of sudden death, overall mortality and recurrent MI in patients with previous MI.
- Alpha-blockers decrease serum cholesterol levels and triglycerides.
- ACE inhibitors and calcium channel blockers are lipid neutral drugs.

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- Patients with HT and dyslipidaemia warrant lipid lowering therapy (statins) just as for patients with CV disease and diabetes.^{34,35,68,134}

Hypertension with obesity and metabolic syndrome

- Prevalence of obesity and hypertension is increasing. Obesity is almost always accompanied by insulin resistance, hyperinsulinemia, impaired glucose tolerance and dyslipidemia. Truncal obesity is more common in Indian population. Also abdominal obesity is associated with sodium retention, endothelial dysfunction, microalbuminuria, LVH and elevated markers of inflammation.
- The diagnosis of metabolic syndrome is made when 3 or more of the following risk determinants are present.^{135,136}

| Table 17: Diagnostic criteria for metabolic syndrome | |
|--|----------------|
| Risk Factor | Defining Level |
| Abdominal obesity (Waist Circumference) | |
| Men | >90 cm |
| Women | >80 cm |
| Triglycerides | ≥150 mg/dl |
| HDL-Cholesterol | |
| Men | <40 mg/dL |
| Women | <50 mg/dL |
| Blood pressure | ≥130/≥85 mm Hg |
| Fasting glucose | ≥110 mg/dL |

- Compared with Whites, Indian men and women have a higher prevalence of central obesity.¹³⁷ Anthropometric parameters of Asians are different than those for white Caucasians and blacks. For example, Asian Indians have smaller body size, excess body fat, and truncal and abdominal adiposity than white Caucasians.¹³⁸ In Asians, the BMI cut-offs for overweight (>23.0 kg/m²) and obesity (>25.0 kg/m²) are lower than WHO criteria. These provisional recommendations will need to be revised in the light of further validation of studies and clinical experience.^{136,139}
- Epidemiological studies have consistently shown a tight correlation between body weight and blood pressure, with 70% of hypertension in men and 60% in women being directly attributable to excess adiposity.¹⁴⁰ Essential hypertension is very frequently associated with a decrease in insulin sensitivity. This insulin resistance is very often associated with dyslipidaemia, obesity, hypertension and impaired glucose tolerance, a cluster termed the “metabolic syndrome or the insulin resistance syndrome.”¹⁴¹
- Lifestyle modification (diet, exercise) is the cornerstone in management of hypertension in obese individuals.
- Dyslipidemia in these patients is characterised by high TG levels and low HDL levels. Such patients require fibrates for control of dyslipidemia.
- Overall, the weight loss effects of sibutramine, anti-obesity drugs do not appear to translate into favourable effects on BP. Instead, sibutramine therapy may be associated with small increases in BP and resting heart rate.¹⁴²
- Obstructive sleep apnea (OSA), now considered a cause of secondary hypertension, is closely associated with obesity. The treatment with of OSA with continuous positive airway pressure (CPAP) has been shown to decrease daytime and nocturnal blood pressures.¹⁴³

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- On the basis of their favourable metabolic profiles, it would appear that ACE inhibitors, ARBs, CCBs and alpha-blockers can decrease blood pressure without worsening the metabolic abnormalities that accompany hypertension in obese patients. ACE inhibitors, low-dose diuretics and non-dihydropyridine CCBs are probably the drugs of first choice in this setting. Alpha-blockers have particular advantages in individuals with dyslipidaemia or glucose intolerance and may be considered as add-on agents. Given that control of hypertension in the majority of hypertensive patients is unlikely to be achieved with any single drug alone, the discussion on choice of drug class may be moot.^{140,142}

Resistant hypertension

- Resistant hypertension is defined as the failure to reach goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic. Table 18 gives causes of resistant HT². These causes can be readily identified and treated. Therefore, the prevalence of true resistant hypertension is low.

Table 18: Causes of resistant hypertension²

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| <ul style="list-style-type: none"> • Volume overload <ul style="list-style-type: none"> - Excess sodium intake - Volume retention from kidney disease - Inadequate diuretic therapy |
| <ul style="list-style-type: none"> • Drug <ul style="list-style-type: none"> - Induced or other causes - Nonadherence - Inadequate doses - Inappropriate combinations - Nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors - Cocaine, amphetamines, other illicit drugs - Sympathomimetics (decongestants, anorectics) - Oral contraceptive hormones - Adrenal steroid hormones - Cyclosporine and tacrolimus - Erythropoietin - Tobacco - Selected over-the-counter dietary supplements and medicines (e.g. licorice and cough syrups) |
| <ul style="list-style-type: none"> • Associated conditions <ul style="list-style-type: none"> - Obesity - Excess alcohol intake |
| <ul style="list-style-type: none"> • Identifiable causes of hypertension <ul style="list-style-type: none"> - Chronic kidney disease - Coarctation of the aorta - Non-specific aortoarteritis - Cushing syndrome and other glucocorticoid excess states including chronic steroid therapy - Obstructive uropathy - Pheochromocytoma - Primary aldosteronism and other mineralocorticoid excess states - Renovascular hypertension - Obstructive sleep apnea syndrome - Thyroid or parathyroid disease |

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Management of resistant hypertension:

Most patients with resistant hypertension need to be referred to specialized hypertension clinics after evaluation of level of compliance. More aggressive salt restriction and elimination of drugs interfering with action of anti-hypertensive agents should be looked at. Subsequently, one should look for secondary hypertension and in case, no secondary cause is found these patients need multiple drugs in high dosages.

Hypertensive crises

Hypertensive crises are classified as hypertensive emergencies or urgencies.

Hypertensive emergencies:

- Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction. They require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage. Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, aortic dissection, or eclampsia.²
- IV nitroprusside is required rarely, in situations like dissection of aorta and subarachnoid haemorrhage with very high blood pressure. It requires intensive care setting and very close monitoring.
- IV nitroglycerine is less effective, but specially useful in patients with ischaemic heart disease and left ventricular failure.¹⁴⁴
- Sublingual captopril, intravenous enalaprilat and/or IV diuretics are useful in hypertensive emergencies, specially in presence of heart failure.

Hypertensive urgencies:

- Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction. Examples include upper levels of stage II hypertension associated with severe headache, shortness of breath, epistaxis, or severe anxiety. The majority of these patients present as noncompliant or inadequately treated hypertensives, often with little or no evidence of target organ damage.²
- The aim should be safe, prompt and gradual lowering of blood pressure without major side effects.¹⁴⁵
- In most urgencies, blood pressure can be controlled with rapidly acting oral medications like calcium channel blockers and ACE inhibitors.
- IV esmolol has been shown to be specially useful for peri-operative accelerated hypertension.
- Sublingual nifedipine should not be used in hypertensive crises as it can cause precipitous fall in blood pressure, reflex tachycardia and may precipitate renal, cerebral or coronary ischaemia.^{2,146}