

# Hypertension in Special Situations

## Hypertension with Diabetes Mellitus

- 30% to 35% of hypertensive patients are detected to have co-existing diabetes mellitus. Similarly, the prevalence of hypertension is 1.5 to 2 times greater in patients with diabetes mellitus as compared to non-diabetics subjects.<sup>111</sup> Co-existence of diabetes and hypertension leads to increased cardiovascular morbidity and mortality. The progress of type 2 diabetes in India is increasing at a very fast pace and this is likely to also contribute to a significant burden of hypertension.<sup>113</sup>
- Blood pressure should be measured on each visit of the diabetic patient and the procedure for measurement is the same as in ordinary hypertensive patients. In diabetic population it is imperative to measure the blood pressure in supine, sitting and standing positions to exclude the possibility of autonomic neuropathy.
- Some of the earlier trials like UKPDS<sup>27</sup> and HOT<sup>26</sup> showed evidence in favour of treating high normal blood pressure aggressively but subsequently, in the ESH/ESC Guidelines 2007, no definitive data was available to substantiate this. Therefore, it is recommended that in high normal blood pressure, more aggressive lifestyle measures should be followed while a blood pressure of more than 140/90 mmHg should be treated with pharmacotherapy to achieve cardiovascular and microvascular protection. In patients with diabetes, blood pressure targets should be less than 140/80 mmHg.<sup>34</sup>
- In the management of diabetic hypertensives, lifestyle modifications have to be more aggressive.
- Lifestyle measures include weight loss in case of obese, dietary changes like low salt and low fat. Regular exercises form the basis and are applicable at all stages of hypertension
- It has been proven that it is useful and effective to treat hypertension in people above the age of 65 years.<sup>114</sup>
- It has been observed that to effectively lower the blood pressure a combination of two or more drugs are required for controlling the blood pressure to target levels. ACE inhibitors in the HOPE trial<sup>169</sup> and ARBs in the ONTARGET trial<sup>163</sup> have emphasised the importance of RAAS blockade to reduce the risk of complications of diabetes, specially microvascular complications and macrovascular complications. Therefore, ACE inhibitors in type 1 diabetes are recommended as the first line drug therapy while ARBs may be used in patients who have type 2 diabetes or who are intolerant to ACE inhibitors.
- CCBs have been shown to be useful as monotherapy and in combination with ACEI in the ASCOT trial.<sup>37</sup> The combination of amlodipine and perindopril was associated with significantly less incidence of new onset diabetes as compared to the combination of  $\beta$ -blocker and diuretic.
- $\beta$ -blockers potentially mask hypoglycemic symptoms.  $\beta$ -blockers are falling into disrepute in an ordinary hypertensive patient but in diabetic population with evidence of coronary artery disease and congestive heart failure they may be quite useful. It is recommended that we may use cardioselective  $\beta$ -blockers like nebivolol and carvedilol.  $\alpha$  blockers can also be used as a useful adjunct in the treatment of the above clinical scenario.
- The ACCORD trial has shown benefits of effective BP control in diabetic patients. It was observed that to prevent one stroke it requires to treat 89 patients with intensive therapy for a period of 5 years.<sup>115</sup>
- The ADVANCE trial<sup>116</sup> and INVEST trial<sup>117</sup> show definitive improvement in the microvascular complications specially on kidneys but their effect on eye and neural complications is questionable. There was a shift towards improvement in macrovascular complications but it did not reach statistical significance.
- The therapy and the targets need to be individualized for each patient depending on age, comorbid conditions, cost factor and socio-psychological factors.
- The drugs which are useful in diabetic pregnant patients who are hypertensive include methyldopa, calcium channel blockers and labetalol. The use of ACE inhibitors/ARBs is contraindicated. Use of diuretics during pregnancy can lead to reduction of plasma volume which can result in low perfusion resulting in decreased fetal growth / fetal damage.

## 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%.<sup>2,28</sup>
- 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 (>220/120 mm Hg). In such patients a cautious reduction in B.P. by 10 to 15% only is suggested.<sup>2</sup>
- BP should not be aggressively reduced in ischemic stroke patients who are otherwise not candidates for thrombolysis. In patients for thrombolytic therapy, SBP > 185 and DBP > 110 mm Hg should be actively treated and maintained below 185/110 mm Hg.<sup>118</sup>
- In acute 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.
- Excessive and sudden elevation of blood pressure 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.<sup>12</sup>
- In acute intracerebral hemorrhage, the SBP and DBP should be maintained below 180/105 mm Hg respectively.<sup>106</sup>
- Hypertensive encephalopathy is an emergency that needs to be identified and aggressively managed
- In stroke survivors with hypertension, blood pressure lowering therapy has been shown to result in 43% reduction in stroke recurrence.<sup>119</sup>
- In the PROGRESS TRIAL, the combination of perindopril and indapamide reduced the risk of stroke by 43% among patients who were hypertensive or normotensive. Perindopril alone was not found to have a similar reduction

in the risk of stroke. Hence, a combination of a ACEI and a diuretic is preferable.<sup>33</sup>

## 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.<sup>2,120</sup>
- 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.<sup>2,121</sup> In more than one half, blood pressure returns to normal when the pill is withdrawn.
- Hormone replacement therapy (low dose estrogen) in post-menopausal women is no longer indicated.

## 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.<sup>122,123</sup>
- 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 and these patients should be observed carefully. The diagnosis of hypertension requires two consecutive measurements of DBP of 90 mm Hg or more.
- Diastolic blood pressure > 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 characterised 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 of pregnancy (Gestational 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.<sup>124</sup>
- The antihypertensive agent used should be efficacious and safe to the mother and the foetus. Methyldopa has been evaluated most extensively and is therefore recommended for women whose hypertension is first diagnosed during pregnancy. Calcium channel blockers (nifedipine), labetalol can be used.<sup>125,126</sup>

- ACE inhibitors, ARBs, and sodium nitroprusside are contraindicated in pregnancy. Use of low dose diuretics is discouraged, since pre-eclampsia is a volume-depleted state.<sup>127</sup>
- Intravenous magnesium sulphate is the drug of choice both for prevention and treatment of seizures.<sup>128,129</sup> Intravenous hydralazine and labetalol are effective agents, but the former is not currently available in India.
- In some cases of eclampsia, 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.<sup>130</sup> A community based study in Mumbai<sup>131</sup> 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. The HYVET trial and HYVET Extension also adds evidence the benefit of BP lowering in the elderly patients and importance of early and sustained antihypertensive treatment even in very elderly people.<sup>132</sup>

In elderly population, systolic hypertension is the commonest form of hypertension. It is a better predictor of cardiovascular/cerebrovascular events, end-stage renal disease and all-cause mortality, as compared to diastolic blood pressure.<sup>133</sup>

### *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.<sup>134</sup>

## 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).<sup>44,135</sup>
- 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.
- Targets for BP control are <140/80 mmHg for those aged 55-79 years. However, for those aged >80 years, a systolic BP of 140-145 mmHg is acceptable.<sup>136</sup>
- Long-acting dihydropyridine CCBs, specially amlodipine, are considered to be the drug of choice in these patients. The CCBs 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, chlorthalidone (6.25 to 12.5 mg per day) or indapamide (1.25-2.5mg per day) can also be

used. Where indicated, these could be combined with ACE Inhibitors or ARBs.<sup>124,137</sup>

- 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).<sup>3</sup> 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.

## Orthostatic Hypotension

This is defined as a fall in the BP of more than 20mm Hg systolic and/or more than 10mmHg diastolic in response to moving from supine to standing position within 3 minutes. Its prevalence is higher in diabetics, elderly, Parkinson's disease. It results in symptoms of lightheadedness, giddiness, blurring of vision or syncope. It may be associated with supine hypertension or a lack of compensatory tachycardia suggestive of autonomic insufficiency. All antihypertensive drugs may produce OH as a side effect, however this occurs more commonly with diuretics,  $\alpha$  blockers, vasodilators and ACEI. OH will influence the selection and continuation of antihypertensive drugs.

Low BP per se is of no significance, however it should be evaluated in the clinical context.

## 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. Heart failure with normal ejection fraction (HF<sub>n</sub>EF) is an entity which is being increasingly recognized now in elderly hypertensives who present with dyspnea. The prevalence of HF<sub>n</sub>EF is equivalent to systolic HF. The prognosis is marginally better than systolic HF. Effective and good control of BP is the mainstay of therapy. Diuretics help in symptomatic improvement in these patients. Other agents like  $\beta$ -blockers and positive inotropes are not useful in these patients.<sup>138,139</sup>

- 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.<sup>140</sup>
- 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.<sup>141-148</sup>

- 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.<sup>59</sup> Other calcium channel blockers are not recommended in these patients.<sup>3</sup>
- 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 Atrial Fibrillation

- Hypertension is an important risk factor for atrial fibrillation. Atrial fibrillation increases the risk of cardiovascular morbidity and mortality by approximately 2 to 5 fold with a marked increase in the risk of embolic stroke. Increased left ventricular mass and enlargement of the left atrium have been identified as independent determinants of new onset atrial fibrillation. Blood pressure control appears to be strictly required when anticoagulant treatment is given because stroke and bleeding episodes are more frequent when systolic blood pressure is >140 mmHg.
- A recent meta analysis shows that there is reduced incidence of new atrial fibrillation in patients receiving an angiotensin receptor antagonist or ACE inhibitor.
- In another recent metaanalysis<sup>149</sup> including almost 12000 patients with systolic heart failure, and therefore at high risk of atrial fibrillation,  $\beta$ -blockers were found to significantly reduce (by about 27%) the incidence of atrial fibrillation. A history of atrial fibrillation and systolic heart failure is therefore a specific indication for using  $\beta$ -blockers.

## Hypertension with Chronic Obstructive Pulmonary Disease

- Hypertension in patients with COPD 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.<sup>3</sup>
- ACE inhibitors have not been found to increase bronchial reactivity in these patients. It is 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 routinely recommended as they are known to exacerbate asthma. However,  $\alpha$ -blockers can be used as add-on therapy in patients with COPD.<sup>150</sup>
- Inhaled corticosteroids and ipratropium bromide can be used safely in these patients.

**Table 19 : 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

## Hypertension with Coronary Artery Disease

Among all the risk factors documented for pathogenesis of CAD, hypertension is reported to be the major risk factor.<sup>133</sup> Blood pressure levels have been shown to be positively and continuously related to the risk of major CAD events.<sup>90</sup>

- 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.<sup>150</sup>
- Amlodipine has been shown to produce subjective and objective improvement in patients with angina.<sup>152</sup>
- Treatment with amlodipine is associated with fewer hospitalisations for unstable angina and revascularisations in patients with angiographically documented CAD.<sup>153</sup>
- Verapamil and diltiazem reduce risk of developing MI following non-Q-wave myocardial infarction.<sup>154</sup>
- After MI, therapy with ACE inhibitors prevents subsequent heart failure and reduces morbidity and mortality<sup>155</sup> ACE inhibitors in combination with digoxin or low dose diuretics, are effective in reducing morbidity and mortality in patients in heart failure.<sup>156</sup>
- Statins and aspirin are recommended in patients with hypertension associated with CAD.

## Hypertension with Dyslipidaemia

Dyslipidaemia often co-exists with hypertension.<sup>157</sup>

- Lifestyle modifications are of particular importance in such patients as they 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.
- ACE inhibitors and calcium channel blockers are lipid

**Table 20 : Causes of resistant hypertension<sup>2</sup>**

- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- Drug
  - 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. liquorice and cough syrups)
- Associated conditions
  - Obesity
  - Excess alcohol intake
- Secondary causes of hypertension
  - 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

neutral drugs and the preferred agents in patients with hypertension in dyslipidemias.

- In high doses diuretics can induce a short-term increase in cholesterol, triglycerides and LDL cholesterol levels. Low dose thiazides do not produce this effect.
- $\beta$ -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.
- Patients with HT and dyslipidaemia warrant lipid lowering therapy (statins) just as for patients with CV disease and diabetes.<sup>31,32,67,158</sup>

## 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 risk determinants are present.<sup>159,160</sup>

- Compared with Whites, Indian men and women have a higher prevalence of central obesity.<sup>161</sup> 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.<sup>162</sup> In Asians, the BMI cut-offs for overweight ( $>23.0$  kg/m<sup>2</sup>) and obesity ( $>25.0$  kg/m<sup>2</sup>) are lower than WHO criteria. These provisional recommendations will need to be revised in the light of further validation of studies and clinical experience.<sup>150,163</sup>
- 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.<sup>164</sup> 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."<sup>165</sup>
- 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.
- 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.<sup>166</sup>
- 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.<sup>154,167</sup>

## 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 of different classes that includes a diuretic.

### Clinical Approach to Resistant Hypertension:

About 12.2% of hypertensive patients have Resistant Hypertension. Ambulatory blood pressure monitoring should be done in these patients in order to classify them as follows:

1. True resistant hypertensives (62.5%),
2. Pseudo or white-coat resistant hypertension (37.5%)

True resistant hypertensive patients are more commonly men, of younger age, with a longer duration of hypertension, smokers, diabetics, target organ damage (including left ventricular hypertrophy, impaired renal function, and microalbuminuria) and overall a worse cardiovascular risk profile.

Therefore, it necessary to assess ambulatory blood pressure monitoring for a correct diagnosis and management of true resistant hypertension.<sup>168</sup>

Table 20 gives causes of resistant HT<sup>2</sup>. These causes can be readily identified and treated.

### 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. Newer intervention-based treatment modalities such as Renal Sympathetic Denervation Therapy and Carotid Baroreceptor Stimulation therapy are under evaluation for management of patients with resistant hypertension. A randomized trial has shown significant BP reduction in patients with resistant hypertension with renal denervation therapy.<sup>76</sup> However, long term follow-up will determine the utility of this therapy.