MANAGEMENT OF HYPERTENSION

Goals of therapy

The primary goal of therapy of hypertension should be effective control of BP in order to prevent, reverse or delay the progression of complications and thus reduce the overall risk of an individual without adversely affecting the quality of life.

Initiation of therapy

Having assessed the patient and determined the overall risk profile, management of hypertension should proceed as follows:

- In low risk patients, institute life style modifications and observe BP for a period of 3 months, before deciding whether to initiate drug therapy.
- In medium risk patients, institute life style modifications and monitor BP on a monthly basis. If after a period of 2-3 months, BP remains above 140/90, then initiate drug therapy.
- In high and very high-risk groups, initiate immediate drug treatment for hypertension and other risk factors.

Targets of therapy

- The earlier concern that lowering DBP too much may increase the risk of coronary events by lowering diastolic perfusion pressure in coronary circulation (J-curve hypothesis) has not been supported by recent studies.[29]
- Gradual reduction of BP is a prudent therapeutic approach except in stage 3 hypertension.
- In Hypertension Optimal Treatment (HOT) study (target diastolic pressure less than 90, 85 or 80 mm Hg) there was no increase in cardiovascular risk in patients randomized to the lowest target group (DBP<80 mm Hg).
- Among diabetic patients participating in the HOT study, there was a significantly lower risk of CAD in patients with the lowest target DBP.[29]
- The results of United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a tight control of BP (average achieved : 144/82 mm Hg) in diabetic patients conferred a substantial reduction in the risk of CAD compared to a less tight control of BP (average achieved: 154/87 mm Hg).[30]
- The PROGRESS trial showed that in patients with a history of stroke or TIA, stroke risk was reduced not only in participants classified as hypertensive, but also among those classified as non-hypertensive, among whom the mean blood pressure at entry was 136/79 mm Hg.[31]
- In view of the above studies, it would seem desirable to achieve optimal or normal BP in young and middle aged. In diabetic subjects (below 130 / 80 mm Hg), or patients with stroke (below 130/85 mm Hg) and at least high normal BP in elderly patients (below 140/90 mm Hg). Antihypertensive therapy should achieve and maintain SBP below 140 mm Hg and DBP below 90 mm Hg and lower if tolerated, while controlling other modifiable risk factors.

Management strategy

- Recent evidence suggests that the level of SBP control correlates better with reduction of mortality than the level of DBP control.[31-39]
- Impressive evidence has accumulated to warrant greater attention to the importance of SBP as a major risk factor for CVDs. The rise in SBP continues throughout life, in contrast to DBP, which rises until approximately 50 years old, tends to level off over the next decade, and may remain the same or fall later in life. Diastolic hypertension predominates before 50 years of age, either alone or in combination with SBP elevation. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.[2]

- Trials describe population averages for the purposes of developing guidelines, whereas physicians must focus on the individual patient's clinical responses".[40]

Non-pharmacologic therapy

Life style measures should be instituted in all patients including those who require immediate drug treatment. These include:

- Patient education: Patients need to be educated about the various aspects of the disease, adherence to life style changes on long term basis and need for regular monitoring and therapy.
- Weight reduction: Weight reduction of even as little as 4.5 kg has been found to reduce blood pressure in a large proportion of overweight persons with hypertension.[41]
- Physical activity: Regular aerobic physical activity can promote weight loss, increase functional status and decrease the risk of cardiovascular disease and all cause mortality. A program of 30-45 minutes of brisk walking or swimming at least 3-4 times a week could lower SBP by 7-8 mm Hg. Isometric exercises such as weight lifting should be avoided as they lead to pressor effects.
- Alcohol intake: Excess alcohol intake causes a rise in blood pressure, induces resistance to antihypertensive therapy and also increases the risk of stroke.[42,43]
- Salt intake: Epidemiological evidence suggests an association between dietary salt intake and elevated blood pressure. The total daily intake of salt should be restricted to 6 gms, however, in hot summer this may be relaxed. Patients should be advised to avoid added salt, processed foods, and salt-containing foods such as pickles, papads, chips, chutneys and preparations containing baking powder. In the Indian context, salt restriction is more important as Indian cooking involves a high usage of salt.

Table 7: Lifestyle interventions for blood pressure reduction (adapted from Chobanian, Hypertension 2003)

Intervention	Recommendation	Expected systolic blood pressure reduction (range)
Weight reduction	Maintain ideal body mass index Below 23 Kg/m^2	5-20 mm Hg per 10 kg weight loss
DASH* eating plan	Consume diet rich in fruits, vegetables, low-fat dairy products with reduced content of saturated and total fat	8-14 mm Hg
Dietary sodium Restriction	Reduce dietary sodium intake to <100 mmol/day (<2.4 g sodium or <6 g sodium chloride)	2-8 mm Hg
Physical activity	Engage in regular aerobic physical activity, for example, brisk walking for at least 30 min most days	4-9 mm Hg
Alcohol moderation	Men≤60 ml per day, twice a week Women≤30 ml per day, twice a week. Abstinence is preferred	2-4 mm Hg
Tobacco	Total abstinence	——

* DASH= Dietary Approaches to Stop Hypertension

- Smoking: Smoking or consumption of tobacco in any form is the single most powerful modifiable lifestyle factor for prevention of major cardiovascular and non-cardiovascular disease in hypertensives.[44-46] Cardiovascular benefits of cessation of smoking can be seen within one year in all age groups.[46]
- Yoga & Meditation: Yoga, meditation and biofeedback have been shown to reduce blood pressure.[47-50]
- Diet:
  - Vegetarians have a lower blood pressure compared to meat eaters[51]. This is due to a higher intake of fruit, vegetables, fibers coupled with a low intake of saturated fats and not due to an absence of intake of meat protein.[52]
  - Intake of saturated fats is to be reduced since concomitant hyperlipidaemia is often present in hypertensives.
  - Regular fish consumption may enhance blood pressure reduction in obese hypertensives.[53]
  - Adequate potassium intake from fresh fruits and vegetables may improve blood pressure control in hypertensives.[54]
  - Caffeine intake increases blood pressure acutely but there is rapid development of tolerance to its pressor effect. Epidemiological studies have not demonstrated a direct link between caffeine intake and high blood pressure.[42]
- Principles of diet in hypertension:[55,56]
  Low calorie, Low fat, Low sodium diet with normal protein intake (0.8 gm / kg body wt)
- Foods with low/moderate content of sodium are recommended. Intake of foods with high potassium content is advisable.

Table 8: Sodium content of foods per 100 gms [55,56]

<25 mg Low		25-50 mg Moderate	50-100 mg Moderately High	>100 mg High
Amla	Cow pea	Raisins	Cauliflower	Amaranth
Bitter gourd	Horse gram	Broad beans	Fenugreek	Bacon
Bottle gourd	Ragi	Carrots	Lettuce	Egg
Brinjal	Vermicelli	Raddish white	Field beans	Lobster
Cabbage	Semolina	Black gram dal	Beetroot	
Lady finger	Wheat	Green gram dal	Water melon	
Colocasia	Maida	Red gram dal	Bengal gram dal	
Cucumber	Milk	Lentil whole	Red gram tender	
French beans	Grapes	Bengal gram whole	Liver	
Peas	Sweetlime	Banana	Prawns	
Onion	Papaya	Pineapple	Beef	
Potato	Orange	Apple	Chicken	
Tomato ripe	Sapota	Mutton		
Yam				

Reduce dietary sodium intake to not more than 6 gm sodium chloride

Table 9: Food items to be avoided in hypertensives[55,56]

A	B
Table Salt	**Salt preserved foods:**
Mono sodium glutamate (Ajinomoto)	Pickles and canned foods
Baking powder	Ketchup and sauces
Sodium bicarbonate	Prepared mixes
Fried foods	Ready to eat foods
Alcohol	**Highly salted foods:**
	Potato chips, cheese, peanut butter, salted butter, papads
	Bakery products: Biscuits, cakes, breads and pastries

Table 10: Foods with high potassium[55,56]

Fruits :		**Vegetables:**	
Amla	Plums	Cabbage	Raddish white
Sapota	Lemon	Bitter gourd	Brinjal
Peaches	Sweetlime	Ladies finger	Pumpkin
Orange	Pineapple	Cauliflower	French beans
Papaya	Apple	Spinach	Colocasia
Banana	Watermelon	Potato	Tapioca
		Drumstick	

Pharmacologic therapy

Principles of drug treatment

- Over the past decade, the goals of treatment have gradually shifted from optimal lowering of blood pressure, which is taken for granted, to patient's overall well being, control of associated risk factors and protection from future target organ damage.[57]
- Achieve gradual reduction of blood pressure. Use low doses of antihypertensive drugs to initiate therapy.
- Five classes of drugs can be recommended as first line treatment for stage 1-2 hypertension[1,2] These include :1) diuretics, 2) beta-blockers, 3) calcium channel blockers, 4) ACE inhibitors, 5) angiotensin II receptor blockers. With regard to lowering of blood pressure, all these five classes are equally effective. The Blood Pressure Lowering Treatment Trialists' Collaboration concluded that treatment with any commonly used regimen reduces the risk of total major cardiovascular events and larger reductions in blood pressure produce larger reductions in risk.[58]
- Low dose diuretics may be preferred as initial therapy unless there are compelling or specific indications for other classes (Table 11).
- Choice of an antihypertensive agent is influenced by age, concomitant risk factors, presence of target organ damage, other co-existing diseases, socioeconomic considerations, availability of the drug and past experience of the physician.
- Combining low doses of two drugs having synergistic effect is likely to produce lesser side effects. In 60-70 % of patients, goal blood pressure will be achieved with two or more agents only.
- Use of fixed dose formulations may be considered to improve compliance.
- If a diuretic is not chosen as the first drug, it is usually indicated as a second step agent because its addition enhances the effects of other agents except dihydropyridine calcium channel blockers.
- Use of long acting drugs that provide 24-hour efficacy with once daily administration ensures smooth and sustained control of blood pressure; which in turn is expected to provide greater protection against the risk of major cardiovascular events and target organ damage. Once daily administration also improves patient compliance.
- Although antihypertensive therapy is generally lifelong, an effort to decrease the dosage and number of antihypertensive drugs should be considered after effective control of hypertension (step-down therapy).
- Due to a greater seasonal variation of temperatures in India, marginal alterations in dosages of drugs may be needed from time to time.
- If addition of a second agent controls blood pressure satisfactorily, an attempt to withdraw the first agent may be considered.

Antihypertensive drugs

Diuretics

Diuretics are widely used as first line agents. They are effective and inexpensive. Although high dose diuretic therapy was associated with side effects, currently recommended low dose diuretic therapy is generally well tolerated. Diuretics should be used in doses equivalent to 12.5 mg daily of hydrochlorothiazide to avoid adverse metabolic consequences. Indapamide use has been shown to be associated with minimal metabolic side effects.

Beta-blockers

Beta-blockers are effective, inexpensive, and relatively well tolerated. These drugs should be avoided in patients with obstructive airway disease and peripheral vascular disease. They also have limitations in patients with dyslipidemia and impaired glucose tolerance. However, they are preferred in young hypertensives, those with stable and unstable angina and post-MI patients with hypertension. Cardioselective beta-blockers (metoprolol) should be preferred over non-selective ones (propranolol). Agents with intrinsic sympathomimetic activity and highly selective beta-blockers such as bisoprolol and nebivolol have lesser metabolic adverse effects. Emerging evidence suggests that beta-blockers are losing their pre-eminent place as first-line antihypertensive agents. This is based on the head to head trials where it was found that beta-blockers are less effective than ACEIs or CCBs at reducing the risk of diabetes and stroke. This was particularly true in patients taking beta-blockers and diuretics. It is observed that in most of these studies, the beta-blocker used was atenolol and in the absence of substantial data on other agents it would not be wise to apply this conclusion to all beta-blockers. The role of beta-blockers could be considered as compelling in certain situations like younger people, those intolerant to ACEIs and ARBs, women of child bearing potential, and people with evidence of increased sympathetic drive. Also, the role of beta-blockers in situations of cardiac decompensation and IHD is not in doubt.

Calcium Channel Blockers (CCBs)

The subgroups of CCBs are dihydropyridines (nifedipine and amlodipine) and non- dihydropyridines (verapamil and diltiazem). Besides blood pressure lowering effect, they also have antianginal effects and are devoid of metabolic side effects. CCBs are particularly recommended for elderly patients with isolated systolic hypertension. Verapamil and diltiazem reduce heart rate and have negative inotropic effects. In the Nordic diltiazem (NORDIL) study,[59] diltiazem was shown to be as effective as treatment based on diuretics, beta-blockers or both, in preventing the combined primary endpoints of stroke, myocardial infarction and cardiovascular deaths. The findings of the recent ASCOT-BPLA (Blood Pressure Lowering Arm) study show that an antihypertensive drug regimen starting with amlodipine (adding perindopril as required) is better than one starting with atenolol (adding thiazide as required) in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and risk of subsequent new-onset diabetes.[39]

Short acting dihydropyridines (nifedipine) should be avoided. Amlodipine has no effect on heart rate and cardiac contractility, and has been shown to be safe even in the presence of congestive heart failure.[60]

Angiotensin Converting Enzyme inhibitors (ACE inhibitors)

ACE inhibitors such as enalapril, lisinopril, ramipril, perindopril, quinapril and others are effective in lowering blood pressure and are well tolerated. These drugs are particularly effective in reducing morbidity and mortality in patients with heart failure and myocardial infarction. In individuals with diabetes mellitus, they retard the onset and progression of renal disease. The HOPE trial (a primary prevention trial) showed that in high and average risk individuals, use of ramipril reduced overall mortality and cardiovascular endpoints, even with small reductions in blood pressure.[61] As a class, they are metabolically favorable. The most common side effect is dry cough. ACE inhibitors are contraindicated in pregnancy. Serum creatinine and potassium should be monitored in patients receiving ACE inhibitors.

Angiotensin II Receptor Blockers (ARBs)

Angiotensin II receptor blockers (losartan, candesartan, valsartan, irbesartan and telmisartan) block the angiotensin II AT-1 receptors, and thus prevent the action of angiotensin II. In the LIFE trial, losartan was better than atenolol in reducing the frequency of the primary composite endpoint of stroke, myocardial infarction and cardiovascular death; this was due to a significant reduction in

stroke.[62] In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, both valsartan and amlodipine reduced blood pressure in hypertensive patients at high cardiovascular risk, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period. The main outcome of cardiac disease did not differ between the treatment groups. The findings emphasize the importance of prompt blood-pressure control in hypertensive patients at high cardiovascular risk.[63] Subgroup analyses of some studies suggests that angiotensin receptor blockers, may marginally increase the rates of myocardial infarction despite their beneficial effects on reducing blood pressure.[64] However, this needs further evaluation. These drugs have many features in common with ACE inhibitors, but do not cause an accumulation of bradykinin. Consequently, cough and angioedema are much less likely to occur than with ACE inhibitors.[9]

Alpha-blockers

Alpha-blockers such as prazosin, terazosin and doxazosin - effectively reduce blood pressure both as monotherapy and in combination. This class of drugs improves insulin sensitivity and has no adverse effects on lipid profile. They have a special place in the management of elderly hypertensives with benign prostatic hyperplasia (BPH).[2,23,65] Since postural hypotension can occasionally occur, the dose of alpha-blockers should be carefully up-titrated. Data from the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) shows that patients in the doxazosin - based arm had 25% increase in the cardiovascular events and twice the risk of congestive heart failure.[66] Alpha-blockers are useful agents for add-on therapy in hypertensive patients with chronic renal failure, peripheral vascular disease, and metabolic disorders. If patients develop heart failure, they should be withdrawn.

Other drugs

Centrally acting drugs have been in use for several years. In particular, methyldopa remains an important agent for the treatment of hypertension in pregnancy. Clonidine, though a potent antihypertensive agent, is infrequently used these days due to side effects such as postural hypotension and problem of withdrawal-related rebound hypertension.

Direct vasodilators such as hydralazine and minoxidil are effective, but some of their side effects (such as tachycardia, headache, and retention of sodium and water) may make it difficult to use them in modern day treatment of hypertension.

Racemic forms of calcium channel blockers and beta-blockers are presently available. However, long-term studies regarding their efficacy and safety are not available.

Table 11 presents guidelines for selecting the most appropriate antihypertensive drugs

Table 12 presents commonly used anti-hypertensive drugs and their usual dosage

Table 11: Guidelines for selecting the most appropriate antihypertensive drugs

Class of drugs	Definite Indication/s	Possible indication/s	Definite contraindication/s	Relative contraindication/s
Diuretics	- Heart failure - Elderly patients - Systolic hypertension	- Diabetes	- Gout	- Dyslipidaemia
Beta-blockers	- Angina - Post-myocardial infarction - Tachyarrhythmia - Heart failure	- Pregnancy - Diabetes	- Asthma and chronic pulmonary disease - Heart block[a]	- Dyslipidaemia - Physically active - Peripheral vascular disease
CCBs	- Angina - Elderly - Systolic hypertension - Diabetes	- Peripheral vascular disease - CVA	- Heart block[b]	- Congestive heart failure[c]
ACE inhibitors	- Heart failure - Left ventricular dysfunction - Post-myocardial Infarction - Significant proteinuria - Diabetes	- CVA	- Pregnancy & lactation - Bilateral renal artery stenosis - Hyperkalemia	- Moderate renal failure (Creatinine levels >3 mg/dl)
Angiotensin II Receptor Blockers (ARBs)	- ACE inhibitor induced cough	- Heart failure - CVA	- Pregnancy & lactation - Bilateral renal artery stenosis - Hyperkalemia	- Moderate renal failure (Creatinine levels >3 mg/dl)
Alpha-blockers	- Prostatic hypertrophy	- Glucose intolerance - Dyslipidaemia	—	- Orthostatic hypotension - Congestive heart failure

[a] Grade 2 or 3 atrioventricular block
[b] Grade 2 or 3 atrioventricular block with verapamil or diltiazem
[c] Verapamil or diltiazem

Table 12: Commonly used anti-hypertensive drugs and their usual dosage

Class	Drug	Dosage (mg/day)
Diuretics	Hydrochlorothiazide	6.25-25
	Chlorthalidone	12.5-25
	Indapamide	1.5-2.5
	Amiloride	5-10
	Triamterene	50-100
	Spironolactone	25-50
Beta-blockers	Atenolol	25-100
	Metoprolol	25-100
	Bisoprolol	2.5-10
	Nebivolol	2.5-5
CCBs	Amlodipine	2.5-10
	Diltiazem	90-360
	Verapamil	80-240
ACE inhibitors	Enalapril	2.5-20
	Lisinopril	2.5-20
	Ramipril	1.25-10
	Perindopril	2-8
	Quinapril	10-80
ARBs	Losartan	50-100
	Candesartan	8-32
	Valsartan	40-160
	Irbesartan	150-300
	Telmisartan	40-160
Alpha-blockers	Prazosin	2.5-10
	Doxazosin	1-4
Centrally acting drugs	Clonidine	0.1-0.3
	Methyldopa	500-1500

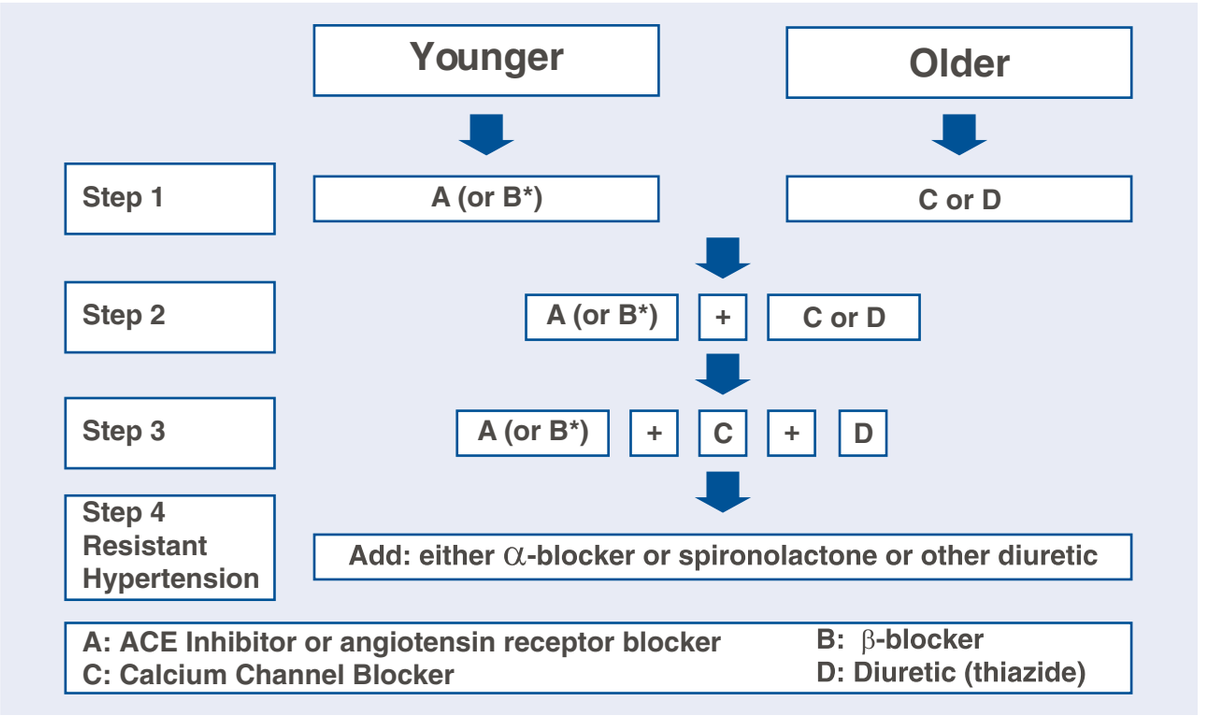
Antihypertensive drug combinations

One often needs to combine different classes of drugs with different mechanisms of action to achieve effective control of blood pressure with minimal side effects. Combinations with additive hypotensive effects will produce greater blood pressure reductions than those obtained with monotherapy. A majority of patients will require two or more drugs for sustained and effective control of blood pressure.[2,9] When a subject is in stage 2 or above, therapy can be initiated either with two drugs or as a fixed dose combination.

Younger individuals have high renin hypertension, hence ACE inhibitors/ARBs or beta-blockers are preferred; while older individuals have low renin hypertension and hence diuretics or CCBs are preferred as first line agents.

In combination, one out of the two groups A [ACE inhibitor/ ARB] or B [beta-blocker] is combined with C [calcium channel blocker] or D [thiazide diuretic] (step 2)
In refractory patients, when 3 agents are to be used, A+C+D is a good choice (step 3)
The combined use of diuretics and beta-blockers is discouraged due to a high incidence of new-onset diabetes.[9]

Figure 1: Algorithm for recommended drug combination



*Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies.

Table 13: Undesirable combinations

- Low dose diuretics and calcium channel blockers
- Beta-blocker and ACE inhibitor
- Beta-blocker and verapamil/diltiazem
- Two drugs from the same class

Drug interactions

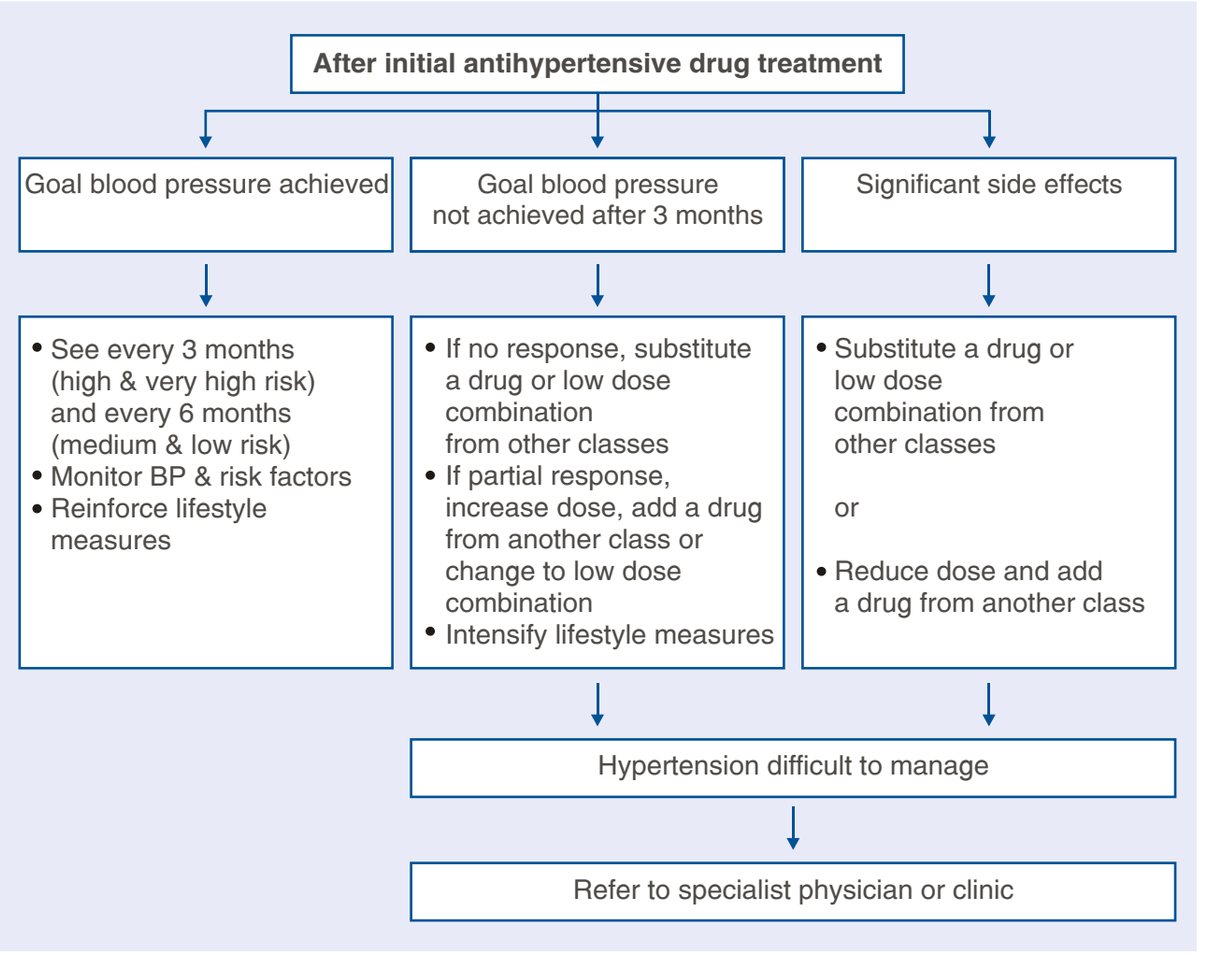
Since multiple drugs are used in hypertensive patients and often these patients have other co-existing conditions, certain common drug interactions should be kept in mind.

Table 14 : Drug interactions

- NSAIDs including COX-2 inhibitors decrease efficacy of diuretics, beta-blockers and ACE inhibitors
- Concomitant use of beta-blockers and non-dihydropyridine CCBs can result in heart blocks
- Combined use of ACE inhibitors and potassium sparing diuretics may result in hyperkalemia
- Cyclosporin levels are increased with diltiazem and verapamil
- Concomitant use of tricyclic antidepressants with methyldopa is to be avoided

Maintenance and follow-up of therapy

Once therapy with particular antihypertensive drugs is instituted, patients need to be seen at frequent intervals during the period of stabilization in order to monitor changes in blood pressure and see whether non-drug measures are being strictly followed. At least once in a fortnight, blood pressure should be measured at the clinic or at home. Other CHD risk factors as well as co-existing diseases/conditions should be monitored. The overall risk category of a patient and the level of blood pressure decide the frequency of follow up visits to a large extent. The frequency can be reduced once blood pressure is stabilized and other risk factors are controlled. Tobacco avoidance must be promoted vigorously.



Adverse drug reactions

Table 15: Checklist for known and common or important side effects with different classes of antihypertensive drugs

Common side effects	Diuretic	-blocker	Calcium channel blocker	ACE inhibitor	ARB	- blocker
Headache	-	-	+	-	-	-
Flushing	-	-	+	-	-	-
Lethargy	-	+	-	-	-	-
Impotence	+	+	-	-	-	-
Cough	-	-	-	+	+	-
Gout	+	-	-	-	-	-
Oedema	-	-	+	-	-	-
Postural hypotension	-	-	-	-	-	+
Cold hands and feet	-	+	-	-	-	-
Hyperkalemia	-	-	-	+	+	-

Associated therapies

In order to reduce the overall risk, patients with hypertension need therapies for control of other risk factors for secondary prevention and now with recent available data even for primary prevention. Low dose aspirin should be prescribed to all hypertensives with cardiovascular disease and stroke (secondary prevention). Hypertensive patients with no previous CV disease but aged >50 years, those with raised serum creatinine, or in high risk group need low dose aspirin for primary prevention. All hypertensive patients with coronary, peripheral, or cerebrovascular disease with LDL levels >100 mg/dL should receive statins as secondary prevention strategies. Hypertensive patients without CV diseases but those in high-risk group should also receive statins for primary prevention. The use of vitamin E and other anti-oxidants has not been shown to be of any benefit in these patients. Hence, their use is not recommended.[67,68]