Special Article

Indian Guidelines on Hypertension - III

With permission from: Hypertension Society of India.

Abbreviations

ABPM – Ambulatory Blood Pressure Monitoring
ACC – Associated Clinical Conditions
ACC/AHA – American College of Cardiology / American Heart Association
ACCELERATE – Aliskiren and Calcium Channel Blocker Amlodipine Combination as Initial Treatment Strategy for Hypertension
ACCOMPLISH – Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ACCORD – Action to Control Cardiovascular Risk in Diabetes
ACEI – Angiotensin Converting Enzyme Inhibitors
ACR – Albumin Creatinine Ratio
ADVANCE – Action in Diabetes and Vascular Disease Perterax and Diamicron MR Controlled Evaluation
AHT – Antihypertensives
ALLAY – Aliskiren in Left Ventricular Hypertrophy Trial
ALLHAT – Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ARB – Angiotensin II Receptor Blockers
ASCOT – Anglo – Scandinavian Cardiac Outcomes Trial
ASCOT-BPLA – Anglo – Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm
BHS – British Hypertension Society
BMI – Body Mass Index
BP – Blood Pressure
BPH – Benign Prostatic Hypertrophy
CAD – Coronary artery disease
CCB – Calcium Channel Blockers
CDUS – Colour Doppler Ultrasound
CKD – Chronic Kidney Disease
COPD – Chronic Obstructive Pulmonary Disease
COX-2 – Cyclo-oxygenase – 2
CPAP – Continuous Positive Airway Pressure
CV – Cardio-vascular
CVA – Cerebro-vascular Accident
CVD – Cardio-vascular Disease
DASH – Dietary Approaches to Stop Hypertension
DBP – Diastolic Blood Pressure
DM – Diabetes Mellitus
DSA – Digital Subtraction Angiography
DTPA – Di-ethylene-triamine-penta-acetate
ECG – Electro-cardiogram
ESC – European Society of Cardiology
ESH – European Society of Hypertension
ESRD – End Stage Renal Disease
GFR – Glomerular Filtration Rate
HBPM – Home Blood Pressure Monitoring
HCWH – Health Care Without Harm
HDL – High Density Lipoprotein
HF – Heart Failure
HFnEF – Heart Failure with normal Ejection Fraction
HOPE – Heart Outcomes Prevention Evaluation
HOT – Hypertension Optimal Treatment Study
hs CRP – Highly sensitive C Reactive Protein
HT – Hypertension
HYVET – Hypertension in Very Elderly Trial
IGH – Indian Guidelines on Hypertension
INVEST – International Verpamil SR/ Trandolapril Study
ISH – Isolated Systolic Hypertension
JNC – Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure
KDIGO – Kidney Disease: Improving Global Outcomes
LDL – Low Density Lipoprotein
LIFE – Losartan Intervention for Endpoint Reduction in Hypertension
LV – Left Ventricle
LVH – Left Ventricular Hypertrophy
MBP – Mean Blood Pressure
MDRD – Modification of Dietary Protein in Renal Disease
MI – Myocardial Infarction
MIBG – Meta-iodo-benzyl-guanidine
MRI – Magnetic Resonance Imaging
NCD – Non communicable diseases
NICE – National Institute for Health and Clinical Excellence
NSAIDS – Non Steroidal Anti Inflammatory Drugs
OH – Orthostatic Hypotension
ONTARGET – Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OSA – Obstructive Sleep Apnea
PET – Positron Emission Tomography
PIH – Pregnancy Induced Hypertension
PP – Pulse Pressure
PRA – Plasma Renin Activity
PROGRESS – Perindopril Protection against Recurrent Stroke Study
PURE Study – Prospective Urban Rural Epidemiology Study
PWV – Pulse Wave Velocity
RAAS – Renin Angiotensin Aldosterone System
RBCs – Red Blood Cells
RF – Risk Factors
RH – Resistant Hypertension
RVH – Renovascular Hypertension
SBP – Systolic Blood Pressure
SHEP – Systolic Hypertension in Elderly Program
TG – Triglycerides
TIA – Transient Ischemic Attack
TOD Target Organ Damage
TONE – Trial of Non-Pharmacological intervensions in the Elderly
UKPDS – United Kingdom Prospective Diabetes Study
VALUE – Valsartan Antihypertensive Long-term Use Evaluation
WHO/ISH – World Health Organization/International Society of Hypertension

Preamble

Hypertension is a major contributor to cardiovascular morbidity and mortality in India and worldwide. In view of our special geographical and climatic conditions, ethnic background, dietary habits, literacy levels and socio- economic variables, there could be some areas where significant differences need to be addressed. With this in mind, the Association of Physicians of India (API), Cardiological Society of India (CSI), the Indian College of Physicians (ICP), and the Hypertension Society of India (HSI) developed the "FIRST INDIAN GUIDELINES FOR THE MANAGEMENT OF HYPERTENSION - 2001."

The second Indian guidelines were published in 2007. Ever since, significant new data on epidemiology of hypertension has emerged globally and so also, from India. Also, many large randomized multi-centric trials have changed practice guidelines and approach to the management of hypertension in the last five years. It was, therefore, felt necessary to update the Indian guidelines to align them with the current best evidence. Hence, the third Indian Guidelines on Hypertension (I.G.H.)-III are being published now in 2013 under the aegis of API.

These guidelines have been prepared as a reference for treating physicians. The current level of practice patterns based on evidence-based medicine have been presented. The intention is not to cover the topic of hypertension in totality but to give useful information based on literature after extensive reference to Medline search and other latest guidelines [JNC VII (2003), ESH/ESC (2007), NICE-BHS (2011), WHO-ISH (2003), ACC/AHA Expert Consensus Document on Hypertension in the Elderly (2011), KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2012)] available to date. These guidelines do not include hypertension in children and adolescents.

The primary aim of these guidelines is to offer balanced information to guide clinicians, rather than rigid rules that would constrain their judgment about the management of individual adult patients, who will differ in their personal, medical, social, economic, ethnic and clinical characteristics.

Methodology

In consonance with the first and second guidelines, a revised format was evolved by the Core committee which was then reviewed by 300 physicians and specialists from across the country whose inputs have been incorporated. Like the previous guidelines, this document has also been studied, reviewed, and endorsed by the Cardiological Society of India (CSI), Hypertension Society of India (HSI), Indian College of Physicians (ICP), Indian Society of Nephrology (ISN), Research Society for Study of Diabetes in India (RSSDI) and Indian Academy of Diabetes (IAD).

We hope these guidelines will help the practising physicians to address to a very important public health problem. Treatment of essential hypertension is a life-long commitment and should not be stopped even when the blood pressure is stabilised without consulting the physician.

The core committee recognizes that the responsible physician's judgment remains paramount for individual adult patients.

What is New in Indian Guidelines on Hypertension - III

- The title of "Indian Guidelines on Hypertension (I.G.H.)-III 2013" has evolved and recommended over the years.
- The health related toxic effects of mercury are recognized world over and mercury sphygmomanometers are being replaced by aneroid and digital sphygmomanometers. We intend to emphasize that the change is inevitable and Indian physicians should also move towards using these devices and wean off the use of mercury sphygmomanometers.
- For follow up of the patients, while in 2nd Indian guidelines use of home monitoring of blood pressure was discouraged. However with availability of better devices and newer data showing its usefulness for follow up of these patients, this is now encouraged.
- The new epidemiological data that is now available in the last five years has been included and reflects the increasing prevalence and poor levels of control of hypertension in India.
- The value of beta-blockers as first line agents in hypertension has receded and these are now recommended as agents for use only in young hypertensives with specific indications. For routine patients these are no longer recommended as first line agents.
- Diuretics are now considered at par with of ACEI's or ARB's and calcium channel blockers and not as preferred agents as in previous guidelines. Chlorthalidone is now available and shown to be better than Hydrochlorothiazide and its usage is to be preferred.
- When blood pressure is high by more than 20/10 mm of Hg systolic and diastolic it is now recommended to start with a combination of drugs. Monotherapy is not going to be effective in achieving target blood pressure.
- Certain combinations have been shown to be better than others in recent trials. Specially ACEI's/ARB's in combination with CCB's forms a good combination.
- Treatment of hypertension even in octogenarians (more than 80 years) has been showed to be beneficial (newer data) and has been recommended.
- At the time of 2nd guidelines, it was felt that "lower the better policy" for target blood pressure was preferred. However it has been realized now that a J shaped curve does exist specially for non revascularised coronary artery disease patients and caution has been advocated in trying to lower blood pressure to low target levels specially in these patients.
- Chronic kidney disease is now recognized as a common comorbidity and has been explained. Awareness and diagnosis of this entity will help recognize the high risk hypertensive individuals.
- Approach to Hypertension and Kidney Disease has been revamped and KDIGO Clinical Practice Guidelines for management of Blood Pressure in Kidney Disease have been included.
- The term HFnEF (Heart Failure with normal Ejection Fraction) needs to be recognized by physicians and has been mentioned and explained for use in clinical practice. HFnEF is common among elderly hypertensive individuals and is diagnosed on the basis of symptoms of dyspnoea, raised BNP levels and diastolic dysfunction on echo with normal ejection fraction.
- Orthostatic Hypotension and its clinical implications have been included.
- A new form of non pharmacological, interventional sympathetic denervation therapy has become recently available and is being evaluated. Its place in treatment of these patients will evolve over a period of time.

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Definition and Classification

Definition

There is a continuous relationship between the level of blood pressure and the risk of complications. Starting at 115/75 mmHg, CVD risk doubles with each increment of 20/10 mm Hg throughout the blood pressure range.[1,2] All definitions of hypertension issued by various international authorities are arbitrary. There is some evidence that the risk of cardiovascular events in Asian Indians is higher at relatively lower levels of blood pressure (BP). In the absence of definite data from India, it would be prudent to maintain the same definition proposed in the first Indian guidelines on management of hypertension (2001).[3]

Hypertension in adults age 18 years and older is defined as systolic blood pressure (SBP) of 140 mm Hg or greater and/or diastolic blood pressure (DBP) of 90 mm Hg or greater or any level of blood pressure in patients taking antihypertensive medication.[1,2]

Classification

The positive linear relationship between SBP and DBP and cardiovascular risk has long been recognized. This relationship is strong, continuous, graded, consistent, independent, predictive and etiologically significant for those with and without coronary heart disease.[4,5] For persons over age 50, SBP is more important than DBP as a CVD risk factor.[6] SBP is more difficult to control than DBP.[7,8] SBP needs to be as aggressively controlled as DBP. Therefore, although classification of adult blood pressure is somewhat arbitrary, it is useful for clinicians who make treatment decisions based on a constellation of factors along with the actual level of blood pressure. Table 1 provides a classification of blood pressure for adults (age 18 and older).[3,9] This classification is for individuals who are not taking antihypertensive medication and who have no acute illness and is based on the average of two or more blood pressure readings taken at least on two subsequent occasions, one to three weeks apart, after the initial screening. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's blood pressure.

The term 'Prehypertension' introduced in the JNC VII guidelines includes a wide range of BP from normal to high normal. It is felt that the term "prehypertension"[2] is more likely to create anxiety in a large subset of population. Hence, we do not recommend the use of the term "pre-hypertension."[9] There is emerging evidence that the high normal group needs to be treated sometimes, in the presence of family history of hypertension and concomitant diseases like diabetes (TOD).[10]

Table 1 : Classification of blood pressure for adults age 18 and older[3,9]

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal**	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension***			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	>180	or	>110
Isolated systolic hypertension			
Grade 1	140-159	and	<90
Grade 2	>160	and	<90

*Not taking antihypertensive drugs and not acutely ill. In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors.
**Optimal blood pressure with respect to cardiovascular risk is below 120/80 mm Hg. However unusually low readings should be evaluated for clinical significance.
***Based on the average of two or more blood pressure readings taken at least on two visits after an initial screening.

Epidemiology of Hypertension

Global[11,12]

As per the World Health Statistics 2012, of the estimated 57 million global deaths in 2008, 36 million (63%) were due to noncommunicable diseases (NCDs). The largest proportion of NCD deaths is caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioral and physiological risk factor to which 13% of global deaths are attributed. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.

Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025. Earlier reports also suggest that the prevalence of hypertension is rapidly increasing in developing countries and is one of the leading causes of death and disability. While mean blood pressure has decreased in nearly all high-income countries, it has been stable or increasing in most African countries. Today, mean blood pressure remains very high in many African and some European countries. The prevalence of raised blood pressure in 2008 was highest in the WHO African Region at 36.8% (34.0–39.7).

The Global Burden of Diseases; Chronic Disease Risk Factors Collaborating Group has reported 35-year (1980-2005) trends in mean levels of body mass index (BMI), systolic BP and cholesterol in 199 high-income, middle-income and low-income countries. Mean systolic BP declined in high and middle-income countries but increased in low-income countries and is now more than in high-income countries. The India specific data are similar to the overall trends in low-income countries.

National[13-25]

The prevalence of hypertension in the late nineties and early twentieth century varied among different studies in India, ranging from 2-15% in Urban India and 2-8% in Rural India.

The historic studies on the prevalence of hypertension in urban and rural India are depicted in Table 2.

Review of epidemiological studies suggests that the prevalence of hypertension has increased in both urban and rural subjects and presently is 25% in urban adults and 10-15% among rural adults (Table 3).

In a meta-analysis of multiple cardiovascular epidemiological studies, it was reported that prevalence rates of coronary artery disease and stroke have more than trebled in the Indian population. In the INTERHEART and INTERSTROKE study, hypertension accounted for 17.9% and 34.6% of population attributable risk of various cardiovascular risk factors for coronary artery disease and stroke respectively.

As per the Registrar General of India and Million Death Study investigators (2001-2003), CVD was the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually. Mortality data from CVD in India are also reported by the WHO. The Global Status on Non-Communicable Diseases Report (2011) has reported that there were more than 2.5 million deaths from CVD in India in 2008, two-thirds due to coronary artery disease and one-third to stroke. These estimates are significantly greater than those reported by the Registrar General of India and shows that CVD mortality is

Table 2: Previous Studies (1963 – 1999) on prevalence of hypertension in Urban and Rural Indian population

Author	Place	Year	Age Group (Years)	Hypertension Criteria (mm Hg)	Prevalence			
					Men		Women	
					%	Sample size	%	Sample size
Urban India								
Mathur	Agra	1963	>20	>160/95	3.98	(1408)	6.64	(227)
Malhotra	Railways	1970	20-58	>160/95	6.2[a] 15.2[b]	(2638) (1594)	—	—
Gupta SP	Rohtak	1978	>20	>160/95	6.00	(1151)	7.00	(872)
Dalal PM	Mumbai	1980	>18	Variable	15.63	(3148)	15.38	(2575)
Wasir	New Delhi	1984	20-60	≥160/95	3.80	(1767)	1.45	(688)
Ahmed	Karnataka	1988	>21	DBP >90	10.20	(698)	2.00	(102)
Hussain	Rajasthan	1988	20-60	>140/90	6.15	(1561)	7.33	(1103)
Chaddha	New Delhi	1990	25-64	>160/90	11.66	(637)	13.68	(7351)
Gupta R	Jaipur	1995	≥ 20	>140/90	30.00	(1415)	34.00	(797)
Rural India								
Gupta SP	Haryana	1977	20-69	>160/95	3.50	(1154)	3.69	(891)
Wasir	Delhi	1983	>20	>160/95	3.20	(441)	7.50	(464)
Baldwa	Rajasthan	1984	21-60	>141/91	6.93	(447)	8.81	(465)
Puri	Himalayas	1986	15-82	>160/95	2.44	(1592)	2.38	(1511)
Hussain	Rajasthan	1988	20-60	>140/90	5.72	(1328)	6.43	(1150)
Kumar	Rajasthan	1991	>21	>160/95	4.00	(3742)	3.60	(3098)
Joshi	Maharashtra	1993	>16	>160/95	4.85	(227)	3.17	(221)
Jajoo	Maharashtra	1993	>20	>160/95	2.89	(2247)	4.06	(1798)
Agarwal	Uttar Pradesh	1994	>20	>160/95	1.57	(3760)	—	—
Malhotra	Haryana	1999	16-70	>140/90	3.00	(2559)[#]	5.80	—

[a]North Indians; [b]South Indians; [#]Overall prevalence and total sample size for men and women; *Overall prevalence for men and women

Table 3 : Recent studies (2000 – 2012) on prevalence of hypertension in urban and rural Indian population

First author	Year	Place	Age (yr)	Sample Size	Prevalence (%)
Urban Population					
Anand MP	2000	Mumbai	30-60	1662	34.0
Gupta PC	2004	Mumbai	≥ 35	88653	47.9
Prabhakaran D	2005	Delhi	20-59	2935	30.0
Reddy KS	2006	National	20-69	19973	27.2
Mohan V	2007	Chennai	≥ 20	2350	20.0
Kaur P	2007	Chennai	18-69	2262	27.2
Yadav S	2008	Lucknow	≥ 30	1746	32.2
Rural Populations					
Hazarika	2004	Assam	>30	3180	33.3
Thankappan	2006	Kerala	>30	2159	36
Krishnan A	2008	Harayana	15-64	2828	9.3
Todkar SS	2009	Maharashtra	≥ 20	1297	7.2
Vijaykumar G	2009	Kerala	≥18	1990	36.1
Bhardwaj R	2010	Himachal	≥ 18	1092	35.9
Kinra S	2010	National	20-69	1983	20.0

Table 4 : Top five causes of deaths in India classified according to areas of residence and gender

Rank	India (all age groups)	Rural populations	Urban populations
1	Cardiovascular	Cardiovascular	Cardiovascular
2	COPD, asthma	COPD, asthma	Cancers
3	Diarrhea	Diarrhea	COPD, asthma
4	Perinatal	Perinatal	Tuberculosis
5	Respiratory infections	Respiratory infections	Senility

Adapted from Registrar General of India Report. COPD: Chronic obstructive pulmonary disease.

increasing rapidly in the country. CVD is the largest cause of mortality in all regions of the country. Table 4 shows the top 5 causes of deaths in the rural and urban populations.

There are large regional differences in cardiovascular mortality in India among both men and women. The mortality is highest in south Indian states, eastern and north eastern states and Punjab in both men and women, while mortality is the lowest in the central Indian states of Rajasthan, Uttar Pradesh and Bihar. The prospective phase of the ongoing Million Deaths Study from 2004-2013 shall provide robust data on regional variations and trends in CVD mortality in India.

The prevalence of hypertension in the last six decades has increased from 2% to 25% among urban residents and from 2% to 15% among the rural residents in India. According to Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, the overall prevalence of hypertension in India by 2020 will be 159.46/1000 population.[25]

Various factors might have contributed to this rising trend, attributable to several indicators of economic progress such as increased life expectancy, urbanization and its attendant lifestyle changes including increasing salt intake and the overall epidemiologic transition India is experiencing currently. Another factor that may contribute is the increased awareness and detection.

The prevalence of high normal blood pressure (also called pre hypertension in JNC-VII) has been seen in many recent studies and was found to be around 32% in a recent urban study from Central India. In some studies from South India (Chennai) and from Delhi prevalence of high normal blood pressure has been even higher upto 36% and 44% respectively in these regions. The prevalence of hypertension increases with age in all populations. In a recent urban study it increased from 13.7% in the 3rd decade to 64% in the 6th decade.

In last 2 decades the prevalence of hypertension has been seen to be static in some urban areas. The prevalence of smoking has declined while that of diabetes, metabolic syndrome, hypercholesterolemia and obesity has been increasing.[26,27]

Hypertension awareness, treatment and control status is low, with only half of the urban and a quarter of the rural hypertensive individuals being aware of its presence. It has been seen that only one in five persons is on treatment and less than 5% are controlled. Rural location is an important determinant of poor hypertension awareness, treatment and control. It has been said that in India the rule- of-halves is not valid and only a quarter to a third of subjects are aware of hypertension.

Preventive measures are required so as to reduce obesity, increasing physical activity, decreasing the salt intake of the population and a concerted effort to promote awareness about hypertension and related risk behaviors. Two upcoming studies for identification of regional differences of CVD risk factors in India are the India Heart Watch and PURE studies. PURE[26] is a prospective study localized to five urban and five rural locations while India Heart Watch[27] has centres all over the country. These studies shall further highlight the prevalence and regional variations of hypertension as a CVD risk factor.

Measurement of Blood Pressure

Clinic Measurement

- Blood pressure (BP) is characterized by large spontaneous variations, therefore the diagnosis of hypertension should be based on multiple BP measurements taken on several separate occasions.
- With increasing awareness about the hazardous effects of mercury on health, the standard mercury sphygmomanometer should be used less frequently, with caution and primarily for calibration of the aneroid and digital sphygmomanometers (to be used in conjunction with stethoscope) which should be used as routine equipments.
- Use a standard cuff with a bladder that is 12 cm X 35 cm. Use a large bladder for fat arms and a small bladder for children. The bladder should encircle and cover 80% of the length of the upper arm. Proper maintenance and calibration of the sphygmomanometer should be ensured. Whenever aneroid sphygmomanometer is used, its accuracy should be checked against standard mercury sphygmomanometer at regular intervals.
- For measurement, inflate the bladder quickly to a pressure 20 mm Hg higher than the point of disappearance of the radial pulse. Deflate the bladder slowly by 2 mm Hg every second.
- The first appearance of the sound (Phase I Korotkoff) is the systolic BP. The disappearance of the sound (Phase V Korotkoff) is the diastolic BP. For children and in those with high output states, muffling of the sound (Phase IV Korotkoff) is taken as diastolic pressure.

Precautions

The following precautions are required for correct measurement of blood pressure:

- At the initial visit, an average of three readings, taken at intervals of 2-3 minutes should be recorded.
- For confirmation of diagnosis of hypertension, record at least 3 sets of readings on different occasions, except in Stage III hypertension.
- Patients should be asked to refrain from smoking or drinking tea/coffee, exercise for at least 30 minutes before measuring the BP.
- Allow the patient to sit for at least five minutes in a quiet room before beginning blood pressure measurement.
- Measurement should be done preferably in a sitting or supine position. Patient's arm should be fully bared and supported at the level of the heart.
- Measure the blood pressure in both arms at the first visit and use higher of the two readings.
- In older persons aged 60 years and above, in diabetic subjects and patients on antihypertensive therapy, the BP should be measured in both, supine/sitting and in standing positions to detect postural hypotension.
- If atrial fibrillation is present, additional readings may be required to estimate the average SBP and DBP.
- Occasionally, thigh BP (popliteal) has to be measured with appropriately large cuff, in prone position especially in younger persons with hypertension. Normally thigh SBP is higher and DBP a little lower than the arm BP because of the reflected pulse wave. This is important for suspected coarctation and nonspecific aortoarteritis, where BP is lower in the lower limb as compared to the upper limb.

Table 5 : Blood pressure thresholds (mm Hg) for definition of hypertension with different types of measurement[23,24]

	SBP (mm Hg)	DBP (mm Hg)
Office or Clinic	140	90
Home (self)	135	85
ABPM (daytime average)	135	85

SBP: *Systolic Blood Pressure;* ***DBP:*** *Diastolic Blood Pressure*

Mercury Manometer as per Recent Guidelines on Environment

In hospitals, mercury sphygmomanometers are usually the equipment that contain largest amount of mercury (70 to 90 grams of mercury).[28] Mercury is a potent neurotoxin, a global priority pollutant and a persistent bio-accumulative. Humans are exposed to methylmercury almost entirely by eating contaminated fish, seafood and wildlife that are at the top of the aquatic food chain.

Health Care Without Harm (HCWH) and the WHO are together leading a global partnership to achieve virtual elimination of mercury-based thermometers and sphygmomanometers over the next decade and their substitution with accurate, economically viable alternatives. This will entail availability of accurate meters for widespread use. This initiative is based on the 2005 WHO Policy Paper, which has set the objective to phase out the demand for mercury-containing fever thermometers and sphygmomanometers by at least 70% by year 2017.

It is recommended that Physicians should gradually look at phasing out the mercury sphygmomanometers and replace these with aneroid and digital meters to be used with stethoscope. Some mercury sphygmomanometers can be kept only for the purpose of calibration.

The other modalities of home BP measurement and ambulatory BP measurement are being recommended by some bodies (NICE guidelines 2011)[29] for diagnosis and definition of hypertension. We feel that with the availability of better automatic home BP monitoring devices, these should be now used increasingly for follow-up of therapy. We may not yet use this for the diagnosis of hypertension.

Home Blood Pressure Measurement

Measurement of blood pressure outside the clinic may provide valuable information for the initial evaluation of patients with hypertension and for monitoring the response to treatment. Home measurement has the advantage that it distinguishes sustained hypertension from "white-coat hypertension", a condition noted in patients whose blood pressure is elevated in the physician's clinic but normal at other times. For home blood pressure, readings of more than 135/85 mm Hg should be considered elevated.

As a change from our second guidelines, we recognize newer data that has emerged indicating that home monitoring of blood pressure (BP) improves compliance and ensures better BP control. We now recommend the use of this modality after proper

patient education regarding its usage and with good quality electronic sphygmomanometers which are periodically checked.

Finger and wrist monitors are inaccurate and are not recommended. The patient should be educated not to change medication without consulting their physician.

Ambulatory Blood Pressure Monitoring

It has been found that at least 20-25% of patients diagnosed with stage I-II hypertension (DBP 90-104 mm Hg) are normotensive outside the physician's clinic. Ambulatory blood pressure monitoring (ABPM) has been found to be clinically useful only in the following settings: to identify non-dippers and white-coat hypertension, evaluate drug resistant hypertension, episodic hypertension, evaluate antihypertensive drugs and in individuals with hypotensive episodes while on antihypertensive medication. However, this procedure should not be used indiscriminately in the routine work-up of a hypertensive patient because of its high cost.

When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension.[29]

BP has a reproducible circadian profile with higher values while awake and mentally and physically active, whereas, much lower values during rest and sleep . Different values have been suggested for definition of hypertension with ABPM for day time average BP (>140/90 mm Hg) and the night-time average (>125/75 mm Hg). Early morning surge in BP for 3 or more hours during transition from sleep to wakefulness, can be an independent risk factor and needs to be managed effectively[22] by addition of a second dose in the evening or a dose of a second class of antihypertensive agent in the evening or a drug with a long half-life.

Pulse Pressure[30]

The Pulse Pressure (SBP-DBP) depends upon factors like arterial stiffness (the cushioning capacity of arteries) and wave reflections - speed of the forward wave (pulse wave velocity of PWV).

MBP is the pressure for the steady flow of blood to peripheral tissues. PP is the consequence of intermittent ventricular ejection from the heart and is influenced by left ventricular ejection fraction and large conduit arteries, mainly the aorta. Factors like arterial stiffness (the cushioning capacity of arteries) and wave reflections – speed of the forward wave (pulse wave velocity or PWV) are also major determinants of PP. In subjects >50 years of age the arterial stiffness and wave reflections become the main determinants of increased SBP and PP.

Novel methods of monitoring central aortic pressure are being developed. Novel therapeutic approaches available to reduce PP and arterial stiffness with age are ACEI or ARBs in association with diuretics.

Evaluation

Evaluation of patients with documented hypertension has three objectives:

- To identify known causes of high blood pressure
- To assess the presence or absence of target organ damage
- To identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment

Data for evaluation is acquired through medical history, physical examination, laboratory tests, and other special diagnostic procedures

Medical History

- Duration and level of elevated blood pressure, if known
- Symptoms of coronary artery disease (CAD), heart failure, cerebrovascular disease, peripheral vascular disease and CKD
- Diabetes mellitus, dyslipidaemia, obesity, gout, sexual dysfunction and other co-morbid conditions
- Family history of high blood pressure, obesity, premature CAD and stroke, dyslipidaemia and diabetes
- Symptoms suggesting secondary causes of hypertension
- History of smoking or tobacco use, physical activity, dietary assessment including intake of sodium, alcohol, saturated fat and caffeine
- Socioeconomic status, professional and educational levels
- History of use / intake of all prescribed and over-the-counter medications, herbal remedies, liquorice (*Yashtimadhu/ Jestamadha*), illicit drugs, corticosteroids, NSAIDs, nasal drops. These may raise blood pressure or interfere with the effectiveness of antihypertensive drugs
- History of oral contraceptive use and hypertension during pregnancy
- History of previous antihypertensive therapy, including adverse effects experienced, if any
- Psychosocial and environmental factors

Physical Examination

- Record three blood pressure readings separated by 2 minutes, with the patient either supine or sitting position and after standing for at least 2 minutes.
- Record height, weight and waist circumference.
- Examine the pulse and the extremities for delayed or absent femoral and peripheral arterial pulsations, bruits and pedal oedema.
- Look for arcus senilis, acanthosis nigricans, xanthelasma and xanthomas.
- Examine the neck for carotid bruits, raised JVP or an enlarged thyroid gland.
- Examine the heart for abnormalities in rate and rhythm, location of apex beat, fourth heart sound and murmurs.
- Examine the lungs for crepitations and rhonchi.
- Examine the abdomen for bruits, enlarged kidneys, masses and abnormal aortic pulsation.
- Examine the optic fundus and do a neurological assessment.

Laboratory Investigations

- Routine
  - Urine examination for protein and glucose and microscopic examination for RBCs and other sediments.

Table 6 : Factors influencing risk of cardiovascular disease

Risk factors for coronary artery disease (RF)	Target organ damage (TOD)	Associated clinical conditions (ACC)
• Age > 55 years*	• Left ventricular hypertrophy detected by ECG and/or echocardiogram	• Cerebrovascular disease
• Male sex	• Microalbuminuria/ proteinuria and/or elevation of serum creatinine (1.2-2.0 mg/ dl)**	- Transient ischemic attack
• Post-menopausal women	• Urinary ACR (albumin creatinine ratio)***	- Ischemic stroke
• Smoking and tobacco use	• Ultrasound or radiological evidence of atherosclerotic plaques in the carotids	- Cerebral haemorrhage
• Diabetes mellitus	• Hypertensive retinopathy	• Heart disease
• Family history of premature coronary artery disease (Males < 55 years, Female < 65 years)		- Myocardial infarction
• Increased Waist:hip ratio		- Angina
• Obesity and Obstructive Sleep Apnoea (OSA)		- Coronary revascularization
• High LDL or Total cholesterol		- Congestive heart failure
• Low HDL cholesterol and High triglycerides		• Renal disease
• High sensitivity C-reactive protein (hs-CRP)		- Diabetic nephropathy
• Estimated GFR <60 mL/min (MDRD)		- Renal failure (serum creatinine > 2.0 mg/dl)
• Lipoprotein-a is a genetic risk factor		• Vascular disease
		- Peripheral arterial disease including non-specific aortoarteritis
		- Aortic dissection
		• Advanced hypertensive retinopathy
		- Haemorrhages or exudates
		- Papilledema

*Coronary artery disease is known to occur 10 years earlier in South Asians than in other ethnic groups.; **Microalbuminuria 30-300mg/24hours; ***Albumin-Creatinine Ratio(ACR) ≥22 (M) or ≥31 (F) mg/g creatinine

Table 7: Risk stratification of patients with hypertension

Stage	Other risk factors and disease history	Blood pressure (mm Hg)		
		Stage 1	Stage 2	Stage 3 (severe hypertension)
		SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP>180 or DBP>110
I	No other risk factors	Low risk	Medium risk	High risk
II	1-2 risk factors[a]	Medium risk	Medium risk	Very high risk
III	3 or more risk factors or TOD[b] or diabetes	High risk	High risk	Very high risk
IV	ACC[c]	Very high risk	Very high risk	Very high risk

Risk strata (typical 10 year risk of stroke or myocardial infarction): Low risk = Less than 15% Medium risk = about 15-20% High risk = about 20-30% Very high risk = 30% or more [a]See Table 6; [b]TOD: Target Organ Damage see Table 6; [c]ACC: Associated clinical conditions, including clinical cardiovascular disease or renal disease see Table 6

- Haemoglobin, fasting blood glucose, serum creatinine, potassium and total cholesterol
- 12-lead electrocardiogram

- Additional investigations in special circumstances can include
  - Fasting lipid profile and uric acid
  - Echocardiogram
- Other specific tests to rule out secondary causes of hypertension where there is a high index of suspicion are described under "secondary hypertension".
- At the present state, tests for hs-CRP and microalbuminuria are not recommended for routine clinical use due to cost considerations. However, for certain situations, these can be useful in risk stratification.
- The cost of investigations in the context of the needs of an individual patient and resources available is an important consideration. In patients with essential hypertension where there is a resource crunch, one may be required to initiate therapy without carrying out any laboratory investigations.

Factors Influencing Risk

Before initiating therapy, patients' overall risk should be assessed considering the presence or absence of additional risk factors; extent of target organ damage and other associated clinical conditions. The presence of one of these three would decrease the threshold for initiation of drug therapy even at lower levels of BP, in that order.

The prognosis of these patients and the choice and need for urgency of therapy, will be dependent on the overall risk stratification (Table 7).

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. Patients should be explained that the lifestyle modifications and drug treatment is generally lifelong and regular drug compliance is important.

Initiation of therapy

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

- In low risk patients, it is suggested to institute life style modifications and observe BP for a period of 2-3 months, before deciding whether to initiate drug therapy.
- In medium risk patients, institute life style modifications and initiate drug therapy after 2-4 weeks, in case BP remains above 140/90.
- In high and very high-risk groups, initiate immediate drug treatment for hypertension and other risk factors in addition to instituting life-style modification.

Targets of therapy

- Gradual reduction of BP is a prudent therapeutic approach except in stage 3 hypertension.

Table 8 : Lifestyle interventions for blood pressure reduction

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 <6 g salt or < 2.4 g sodium.	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

Table 9 : Sodium content of foods per 100 gms[54,55]

<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	Reddish 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				

Table 10 : Food items to be avoided in hypertensives[54,55]

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

- 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).[31]
- Among diabetic patients participating in the HOT study, there was a significantly lower risk of coronary artery disease in patients with the lowest target DBP.[31]
- 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 Coronary Artery Disease compared to a less tight control of BP (average achieved: 154/87 mm Hg).[32]

Table 11 : Foods with high potassium[54,55]

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

- 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.[33]
- In view of the above studies, it would seem desirable to achieve optimal or normal BP (<140/90 mHg) in the young and middle aged. In diabetic patients BP lowering to around 140 / 80 mm Hg is recommended. In patients who have survived stroke, a BP of around 130/85 mm Hg is suggested. In elderly patients a high normal BP around 140-145/90mm Hg should be taken as the target BP.[34]
- Initially the J-shaped hypothesis was accepted, and it was felt that lowering BP below a certain level (140/90 mmHg) would increase the risk of coronary events by lowering diastolic perfusion pressure in coronary circulation. Data from the HOT study and UKPDS study showed BP reduction to levels of 130/80 specially in high-risk individuals (diabetics, CKD, and CVA) was more beneficial. Hence, at the time of second guidelines it was suggested that the lower the better policy holds true for target BP in hypertension. More recent data (ADVANCE,ACCORD,INVEST) shows lowering of diastolic BP to below 70 mmHg can be deleterious, specially in patients with coronary artery disease.[115-117]
- As compared to the previous guidelines of 2007, we now realize that a relatively less aggressive approach towards achieving lower target BP is a reasonable goal, since as suggested above, recent data shows no additional benefit of lowering diastolic BP below certain levels in specific situations.

Management Strategy

- Recent evidence suggests that the level of SBP control correlates better with reduction of mortality than the level of DBP control.[28,35-42]
- 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 of age. It 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.[43]

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.[44]
- 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.[45,46] Alcohol consumption should be limited to no more than 2 drinks per day (24oz beer, 10oz wine, 3oz 80-proof whiskey) for most men and no more than 1 drink per day for women and lighter weight people.[2]
- 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 (amounting to 3-4 gms of sodium), 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.
- 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.[47-49] Cardiovascular benefits of cessation of smoking can be seen within one year in all age groups.[44]
- Yoga and Meditation: Yoga, meditation and biofeedback have been shown to reduce blood pressure.[50-53]
- Diet:
  - Vegetarians have a lower blood pressure compared to meat eaters.[54] 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.[55]
  - 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.[56]
  - Adequate potassium intake from fresh fruits and vegetables may improve blood pressure control in hypertensives.[57]
  - Caffeine intake increases blood pressure acutely but there is rapid development of tolerance to its pressor

Table 12a : Guidelines for selecting the most appropriate first- line 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
β –blockers	Angina Post-myocardial infarction Tachyarrhythmia Heart failure	Pregnancy Diabetes	Heart block	Dyslipidaemia Physically active Peripheral vascular disease Elderly persons > 50 years Asthma and chronic pulmonary disease (COPD)
CCBs	Metabolic syndrome Angina Elderly Systolic hypertension Diabetes	Peripheral vascular disease CVA	Heart block[a]	Congestive heart failure[a]
ACE inhibitors	Metabolic syndrome Heart failure Left ventricular dysfunction Post-myocardial Infarction Significant proteinuria Diabetes	CVA	Pregnancy and lactation Bilateral renal artery stenosis Hyperkalemia	Moderate renal failure (Creatinine levels >3 mg/dl)
Angiotensin II Receptor Blockers (ARBs)	Metabolic syndrome Diabetes mellitus Proteinuria LV dysfunction ACE inhibitor induced cough	Heart failure CVA	Pregnancy and lactation Bilateral renal artery stenosis Hyperkalemia	Moderate renal failure (Creatinine levels >3 mg/dl)

[a]Verapamil or diltiazem

Table 12b: Guidelines for other drugs

Class of drugs	Definite Indication/s	Possible indication/s	Definite contraindication/s	Relative contraindication/s
α blockers	Prostatic hypertrophy Chronic Kidney Disease	Glucose Intolerance Dyslipidemia	Orthostatic hypotension Congestive Heart Failure	
Centrally acting agents				
α methyldopa	Hypertension in Pregnancy	Resistant Hypertension	Acute or Chronic Liver Disease	
Clonidine	Resistant Hypertension	CKD	Pregnancy, Lactation	
Vasodilators	Resistant Hypertension Hypertension in Pregnancy			Coronary Artery Disease
Direct renin inhibitors				
liskiren	Resistant Hypertension		Pregnancy Lactation B/L Renal Artery Stenosis Hyperkalemia	Moderate Renal Failure (Creatinine > 3mg/dl)

effect. Epidemiological studies have not demonstrated a direct link between caffeine intake and high blood pressure.[58]

- Thus, the diet in hypertensives should be low calorie, low fat, and low sodium, with normal protein intake.[59,60]

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.[61]
- 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) ACE inhibitors, 2) angiotensin II receptor blockers, 3) calcium channel blockers, 4) diuretics and 5) newer β-blockers.
- 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.[62]
- 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 or more drugs having synergistic effect is likely to produce lesser side effects. In

Table 13 : Anti-hypertensive drugs and their usual dosage

Class	Drug	Dosage (mg/day)	Dosing frequency/Day
Diuretics	Hydrochlorothiazide	6.25-12.5	1–2
	Chlorthalidone	6.25-12.5	1
	Indapamide	1.5-2.5	1
	Amiloride	5-10	1–2
	Triamterene	50-100	1–2
	Spironolactone	25-50	1–2
β -blockers	Metoprolol	25-100	1–2
	Bisoprolol	2.5-10	1
	Nebivolol	2.5 - 5	1
α + β Blocker	Carvedilol	3.125 – 50	2
	Labetalol	50 -200	2
CCBs	Amlodipine	2.5-20	1
	Cilnidipine	5 - 10	1
	Diltiazem	90-360	1
	Nifedipine (Long-acting)	10 - 40	1
	Verapamil	80-240	1-2
Racemic isomers	S-amlodipine	2.5 - 10	1
ACE inhibitors	Enalapril	2.5-20	1-2
	Lisinopril	2.5-20	1
	Ramipril	1.25-10	1-2
	Perindopril	2-8	1-2
	Quinapril	10-80	1-2
ARBs	Losartan	50-100	1-2
	Candesartan	8-32	1-2
	Valsartan	40-160	1
	Irbesartan	150-300	1
	Telmisartan	40-160	1
	Olmesartan	20 - 40	1
α -blockers	Prazosin	2.5-10	2-3
	Doxazosin	1-4	1
Centrally acting drugs	Clonidine	0.1-0.3	2
	Methyldopa	500-1500	2
	Moxonidine	0.2-0.4	1-2
Vasodilators	Hydralazine	25-100mg	2
	Minoxidil	2.5-5mg	1-2
Direct renin inhibitors	Aliskiren	150-300	1

60-70 % of patients, goal blood pressure will be achieved with two or more agents only.

- Use of fixed dose formulations should be considered to improve compliance.
- Drugs with synergistic effects should be combined pertinently to enhance BP lowering effect so as to achieve target BP.
- 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.

Antihypertensive drugs

Angiotensin Converting Enzyme inhibitors (ACE inhibitors)

ACE inhibitors are effective in lowering blood pressure and are well tolerated. These are first line agents in post-MI patients, those with heart failure, diabetes, and in patients with other metabolic risk factors. In individuals with diabetes mellitus, they retard the onset and progression of renal disease (patients with microalbuminuria and early CKD). 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.[63] 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. Ramipril and Perindopril have greater tissue ACE inhibition effect than other agents. Perindopril in combination with Indapamide has been particularly shown to reduce mortality in patients who have survived stroke (PROGRESS trial).[33]

Table 14:Adverse drug reactions for first-line drugs

Common side effects	ACE inhibitor	ARB	Calcium channel blocker	Diuretic	B-blocker
Headache	-	-	+	-	-
Flushing	-	-	+	-	-
Lethargy	-	-	-	-	+
Impotence	-	-	-	+	+
Dry cough	+	+/-	-	-	-
Gout	-	-	-	+	-
Oedema	-	-	+	-	-
Postural hypotension	+	+	-	+	-
Cold hands and feet	-	-	-	-	+
Hyperkalemia	+	+	-	-	-
Hyperglycemia				+	+
Dyslipidemia				+	+
Angioedema	+	+			

Angiotensin II Receptor Blockers (ARBs)

Angiotensin II receptor blockers 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.[64] 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.[65] 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] Initially, some fears were raised regarding increase of coronary events with use of these agents, however, these have been disproved ever since. Also, one retrospective meta-analysis suggested increase in neoplasm with ARBs, however no prospective study has suggested this and is generally believed not to be a significant issue at present. In fact, the ONTARGET trial shows telmisartan (80mg OD) is as effective as ramipril (10mg OD) in reducing CV events in high-risk individuals in patients with vascular disease or high-risk diabetes. Also, the incidence of angioedema was less than with ramipril.[66] A combination of ACE and ARB should not be used due to increased risk of hypotension and hyperkalemia. In the recent randomized double blind ROADMAP[68] trial involving 4447 diabetic patients with olmesartan (40mg OD), the onset of microalbuminuria has been shown to be delayed in patients with type 2 diabetes.

Calcium Channel Blockers (CCBs)

The two subgroups of CCBs are dihydropyridines (amlodipine, felodipine, nifedipine, cilnidipine) and non- dihydropyridines (verapamil and diltiazem). Amlodipine is the most commonly used agent in this group. 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 trial,[67] diltiazem was shown to be as effective as treatment based on diuretics, β-blockers or both, in preventing the combined primary endpoints of stroke, myocardial infarction and cardiovascular deaths. The findings of the 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.[37]

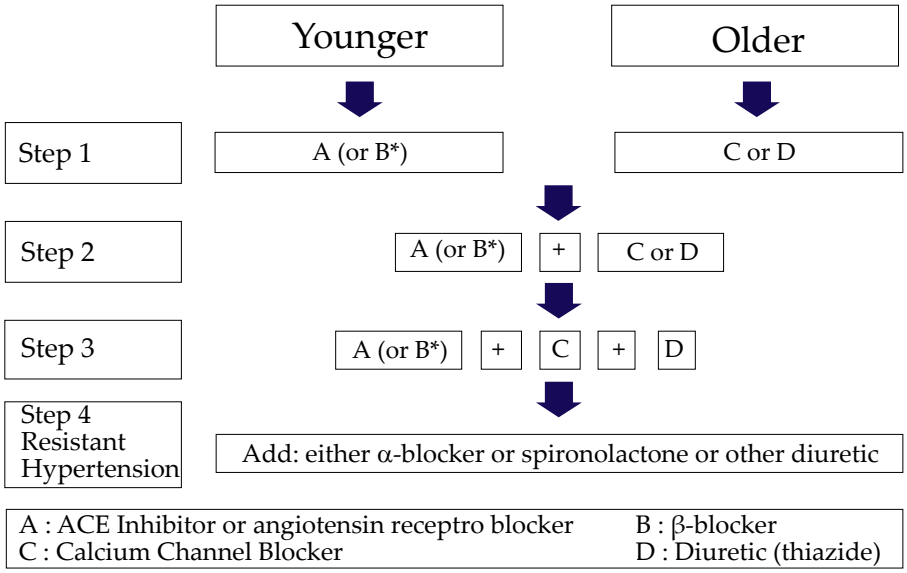
Short acting dihydropyridines (nifedipine) should be avoided. Amlodipine has no effect on heart rate and cardiac contractility, and has been shown to be safe even in the presence of congestive heart failure.[69]

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. Low dose diuretics have lesser metabolic side effects like worsening of glycemic control, hyperuricemia and dyslipidemia. Diuretics should be used in doses equivalent to 12.5 mg daily of chlorthalidone or hydrochlorothiazide to avoid adverse metabolic consequences. Chlorthalidone is preferred over hydrochlorothiazide as an antihypertensive.[70] Indapamide use has been shown to be associated with minimal metabolic side effects and is a useful agent. Combinations of thiazides and potassium-sparing diuretics are available and are effective options. Aldosterone antagonists (Spironolactone, Eplerenone) are being increasingly used as add-on agents to reduce BP in patients with resistant hypertension even without documenting hyperaldosteronemia. In cases of heart failure and/or renal failure, Furosemide (40-80mg), Torsemide (10-40mg), Metolazone (2.5-5mg) can be used as add-on therapy.

Newer β -blockers

Emerging evidence suggests that β-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 β-blockers are less effective than ACEIs or CCBs at reducing the risk of diabetes and stroke. This was particularly true in patients taking β-blockers and diuretics. In most of the studies, the β-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 β-blockers. β - blockers reduce central aortic pressure to a lesser extent than other classes and this is additional reason for lack of mortality reduction with their use. They also have limitations in patients with dyslipidemia and impaired glucose tolerance. However, they are used in young hypertensives, those with stable and unstable angina and post-MI patients with hypertension. Agents with intrinsic sympathomimetic activity and highly selective β-blockers such as bisoprolol and nebivolol have lesser metabolic adverse effects. Labetalol is an



*Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies. Use β blockers only in special situations. B = Newer β blockers. Younger age: <55 years, Older: >55 years

Fig. 1 : Algorithm for recommended drug combination

α and β blocker and can be particularly used in hypertension in pregnancy.

Other drugs

α-blockers: Prazosin, terazosin and doxazosin - effectively reduce blood pressure both as monotherapy and in combination. They have a special place in the management of elderly hypertensives with benign prostatic hyperplasia (BPH) and CKD.[2,71,72] Since postural hypotension can occasionally occur, the dose of α-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.[73]

Centrally acting drugs : A-methyldopa, clonidine and moxonidine - 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. These agents are used in CRF patients with resistant hypertension.

Direct vasodilators : 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.

Direct renin inhibitors: Aliskiren - has been evaluated and found to be effective. In the ALLAY trial, aliskiren was found to be as effective as losartan in regressing LVH.[74] In the more recent ACCELERATE trial,[75] combination of aliskiren and amlodipine was found to be more effective than monotherapy. It is a useful agent in resistant hypertension and also reduces the proteinuria in diabetes with hypertension.

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

Newer modalities: A novel baroreflex activation therapy has been evaluated recently. It stimulates baroreceptors through an implanted device and has been shown to reduce significant change in BP in patients with resistant hypertension. Renal sympathetic denervation therapy has been evaluated in which radiofrequency ablation of sympathetic plexus around renal arteries is performed. In the SYMPLICITY hypertension -2 trial,[76] it has been shown to reduce BP significantly over and above the pharmacological therapy. Presently, both these modalities are under evaluation for management of patients with resistant hypertension.

Table 12a and 12b presents guidelines for selecting the most appropriate antihypertensive drugs. Table 13 presents commonly used anti-hypertensive drugs and their usual dosage.

Table 14 lists some common side effects of these drugs.

Antihypertensive Drug Combinations

Combination therapy is gaining ground for effective control of hypertension since a majority of patients will require two or more drugs for sustained and effective control of blood pressure.[2,9]

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. When a subject is in stage 2 or above, therapy can be initiated either with two drugs or as a fixed dose combination. The ACCOMPLISH trial has shown that combination of ACEIs with CCBs is better than a combination of ACEI with diuretic and should be the preferred combination.[77]

Younger individuals have high renin hypertension, hence ACE inhibitors/ARBs or newer β-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/

Table 15: Undesirable combinations

- B-blocker and ACE inhibitor
- B-blocker and centrally acting drugs
- B-blocker and verapamil/diltiazem
- ACE inhibitors and ARBs
- Two drugs from the same class

ARB] or B [β-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).[9]

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.

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 and alcohol moderations must be promoted vigorously.

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). 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.[79,80]

Table 16 : Drug interactions[78]

ACE inhibitors, diuretics and β-Blockers
NSAIDs including COX-2 inhibitors decrease efficacy of diuretics, β-blockers and ACE inhibitors
Calcium channel blockers
Verapamil increases the blood levels of several statins, such as atorvastatin, simvastatin and lovastatin
Nifedipine is broken down by hepatic CYP3A4 system. Cimetidine inhibits the CYP3A4 system and thus the breakdown of nifedipine also potentially increases blood levels and antihypertensive effects. Conversely, phenobarbital, phenytoin and rifampin induce the CYP3A4 system to metabolise nifedipine, so that blood levels should fall
Amlodipine should not be used with statins such as simvastatin, atorvastatin or lovastatin since both drugs are metabolised by hepatic CYP3A4 system
Cyclosporin levels are increased with diltiazem and verapamil
Diuretics
Steroids can worsen diuretic-induced hypokalemia. Steroids also produce sodium retention which antagonises the main effect of diuretics that is natriuresis.
Antiarrythmics of Class 1A (quinidine or procainamide) or Class III (sotalol, amiodarone) can prolong QT interval and may precipitate torsade de pointes in presence of diuretic-induced hypokalemia
ACEI or ARBs which retain potassium can counteract the potassium loss of diuretics. This is a favourable drug interaction
Combined use of ACE inhibitors or ARBs and potassium sparing diuretics may result in hyperkalemia
β blockers
Metoprolol and carvidelol metabolism is inhibited by paroxetine (Selective serotonin receptor blocker – antidepressant) and propoxyphene (opoid analgesic) resulting in increased antihypertensive effect
β blockers and non-dihydropyridine CCBs
Heart Blocks
***α* methyldopa**
Concomitant use of tricyclic antidepressants with methyldopa is to be avoided

Secondary Hypertension

The prevalence of secondary hypertension is around 5-6% of all hypertensives. Because of low prevalence, routine screening for secondary hypertension is not essential and cost effective. Renal disease constitutes the major group of secondary hypertension.

When to suspect secondary hypertension clinically?

- Absence of family history of hypertension
- Severe hypertension > 180/110 mm Hg with onset at age < 20 years or > 50 years
- Difficult-to-treat or resistant hypertension with significant end-organ damage features
- Combination of pain (headache), palpitation, pallor and perspiration – 4 P's of phaeochromocytoma
- Polyuria, nocturia, proteinuria or hematuria – indicative of renal diseases
- Absence of peripheral pulses, brachiofemoral delay and abdominal or peripheral vessel bruits
- History of polycystic renal disease or palpable enlarged kidneys
- Cushingoid features, multiple neurofibromatosis
- Significant elevation of plasma creatinine with use of ACE inhibitors
- Hypertension in children
- History of snoring, daytime somnolence, obesity, short and thick neck – Obstructive Sleep Apnoea

A. **Hypertension in Chronic Kidney Diseases**

Hypertension, after diabetes mellitus, is the second leading cause of end-stage renal disease (ESRD) and together these entities account for over 60% of ESRD patients.[83] Essential hypertension is an important cause of chronic kidney disease and renal parenchymal disease is a well established cause of secondary hypertension.

There are two forms of kidney diseases causing hypertension namely renal parenchymal and renovascular.

Causes:

Renal parenchymal diseases – (Non-diabetic)[84,85]

Table 15 : The percentage prevalence of various causes of Hypertension[81,82]

A. Primary or Essential	94-95%
B. Secondary	
Renal	
Renal parenchymal	2-3%
Renovascular	1-2%
Endocrinal	0.3-1%
Primary aldosteronism	
Phaeochromocytoma	
Cushing's Syndrome	
Acromegaly	
Vascular – Coarctation of aorta Nonspecific aortoarteritis	
Drugs – Oral Contraceptives, NSAIDs Steroids, Cyclosporine	0.50%
Miscellaneous Obstructive Sleep apnoea	0.50%
Chronic glomerulonephritis	
Chronic interstitial nephritis	
Analgesic nephropathy	
Polycystic kidney disease	
Gout with renal failure	
Obstructive nephropathy	

Stages of Chronic Kidney Diseases and Action Plan

The functional stages are based on estimated GFR in CKD with the relevant action plan as below.[86]

Treatment

Therapy with antihypertensives in CKD has been found to not only control BP but also slows down the progression of chronic kidney diseases. The Ramipril Efficacy in Nephropathy (REIN), ACEI and progressive Renal Insufficiency (AIPRI) and modification of Dietary Protein in Renal Disease (MDRD) trials established the ability of antihypertensives to slow down the progression of non-diabetic chronic kidney disease.[87-90]

1. Threshold for initiation of AHT[2]
   a. BP 140/90 Hg for patient without proteinuria
   b. BP 130/80 for those with proteinuria

   Target to achieve: BP < 130/80mmHg

In post renal transplant patients, hypertension is an important issue since certain drugs like cyclosporine and erythropoietin used in these patients can aggravate hypertension. At times, combination of multiple drugs

Table 16 : Staging System and Action Plan for Chronic Kidney Disease

Stage	Description	GFR[#] (mL/min per 1.73 m^2)	Action[*]
–	At increased risk for CKD	≥ 90 with risk factors[Ψ]	Screening CKD risk reduction
1	Kidney damage[¥] with normal or increased GFR	≥ 90	Diagnosis and treatment. Retard progression of CKD. Treat comorbidities. Cardiovascular disease risk reduction.
2	Mild decrease in GFR	60-89	Estimate progression
3	Moderate decrease in GFR	30-59	Evaluate and treat complications
4	Severe decrease in GFR	15-29	Prepare for renal replacement therapy
5	Kidney failure	< 15 or dialysis	Renal Replacement Therapy if uremic

[#]Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula: GFR (mL/min/1.73 m 2) = 186 x (Pcr)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if African American)
*Includes actions from preceding stages.
[Ψ]Risk factors : hypertension, dyslipidemia, diabetes mellitus, anemia, systemic lupus erythematous, chronic analgesic ingestion.
¥Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine or imaging tests.

incuding ACEI, ARB, CCB and diuretics may be required for effective BP control. In patients where BP is still not controlled, clonidine, α methyl dopa or α blockers may be added.

Renovascular:

- The most common cause of renovascular hypertension in India is Takayasu's syndrome (progressive aortoarteritis),[91] though atherosclerotic renovascular disease is also being recognised more often now in early patients.
- The most common cause of renovascular disease in Western population are atherosclerotic disease in 60% of elderly population and fibromuscular dysplasia in 35% of young. Atherosclerotic renal artery stenosis have associated cardiovascular disease.
- Rare causes include embolic and tumor, thrombus and extrinsic reasons.
- Takayasu's disease is a non-specific panarteritis affecting young women. Hypertension is mainly due to renal artery stenosis which can be unilateral or bilateral.[92]
- Renovascular disease is much more common than renovascular hypertension (RVH).
- Atherosclerotic disease involves the proximal segment and fibromuscular dysplasia involves the distal segment of renal artery.

Investigations :

- A paraumbilical bruit is heard in 50-60% of patients with renovascular hypertension and 10% cases of essential hypertension. A diastolic renal bruit is more specific than systolic bruit.
- In patients with moderate degree of suspicion of renovascular hypertension, non-invasive tests are recommended initially.
- Wherever there is a high degree of suspicion, direct selective renal arteriography is recommended.
- Colour Doppler Ultrasound (CDUS), CT angiography and MRI angiography are other good and non-invasive modalities. MRI angiography has higher sensitivity (90%) and specificity (92%).
- ^{99}Tc – DTPA and ^{123}I – Hippuran scan are useful non-invasive investigations. These tests give functional status of CKD.
- Conventional angiography, though invasive, is the gold standard. Intra-arterial injection with digital subtraction angiography (DSA) may be used. Once the diagnosis is confirmed, renal angioplasty with stenting is the treatment of choice. Physicians should confirm anatomical narrowing versus functional disturbances before embarking upon planning any intervention. When angioplasty is not possible, surgical approach is recommended.

Treatment of renal artery stenosis

Goals are control of BP and preservation of renal function. In general there are three options. :

Medical

Percutaneous transluminal renal angioplasty

Surgery

Patients with fibromuscular dysplasia benefit from angioplasty or surgical revascularisation. Patients with atherosclerotic renovascular disease do not demonstrate any significant benefit from renal artery intervention but medical therapy is equally effective in these patients.[92]

B. Endocrine causes

1. Pheochromocytoma

   These chromaffin cell tumors are mostly adrenal. These may be extra-adrenal in 15% of the cases and bilateral adrenal in 10% of the cases. 10% of all cases are familial and 10% are malignant.

   Episodic hypertension, postural fall, pallor, throbbing headache, palpitations and perspiration are suggestive clinical features.[94]

Investigations

- Screening tests include plasma and urinary biochemical assay for free catecholamines, metanephrines and vanillyl-mandelic acid (VMA). These tests have high specificity (99%) and sensitivity (85-90%). Following drugs should be withdrawn for 48 hours before doing these tests: α methyldopa, β blockers, clonidine, penicillin and certain vegetables. Patients can be continued on CCBs and ACE inhibitors during evaluation. .
- Tumor localisation: Computed Tomography scan and MRI of the abdomen have greatly simplified tumor localisation; MIBG labelled with I^{131} is the most specific way of diagnosing adrenal and extra adrenal pheochromocytomas.[95] Other modalities include PET scan using^{18} F-fluorodeoxy glucose.
- Once localised, surgery should be offered to all the patients. Mortality from surgery is now less than 5%. For pre-operative preparation, control of blood pressure is important and can be achieved with oral phenoxybenzamine 10 mg once daily, to be increased slowly. Oral prazosin and terazosin preferentially block post-synaptic α1-receptors on vessel wall and leave pre-synaptic α 2- receptors. As a result, tachycardia is less of a problem. B-blockers may be given to these patients to control tachycardia and arrhythmias, only after α-blockers have been started.

2. Primary Aldosteronism

   Primary aldosteronism is due to excess aldosterone secretion by the adrenal cortex secreted generally by adenomas and occasionally due to bilateral adrenocortical hyperplasia. This is suspected in a case of hypertension showing persistent hyokalaemic metabolic alkalosis in the absence of diuretic therapy. Plasma Aldosterone to Plasma Renin Activity (PRA) ratio more than 20 to 25 (normal < 10) is 95% sensitive and 75% specific for Primary Hyper Aldosteronism. It is usually diagnosed by imaging techniques.

3. Cushing's Syndrome

   Hypertension is present in approximately 80% of patients with Cushing's syndrome. Other clinical features include central obesity, hirsutism, polycythaemia and pink striae on the abdomen. This can be screened by performing early morning serum cortisol levels. Hypertension remits in most patients after successful treatment.

c. Miscellaneous

Other important secondary causes include:

- Oral contraceptives (see Hypertension in Women pg. no. 29)
- Coarctation of aorta, a congenital disease needs surgical correction
- Thyroid disorders, both hypothyroidism and hyperthyroidism
- Sleep apnea syndrome is one of the common causes of reversible hypertension. Polysomnography is diagnostic. No specific drugs have proven superior in sleep apnea but use of C-PAP improves the hypertension
- Acute stressful situations cause intense sympathetic discharge and may temporarily induce hypertension. B blockers are preferred.
- Common conditions include acute mental stress, hypoglycaemia, acute intermittent porphyria, exposure to cold, burns, perioperative period and post head injury
- Drugs: Non-steroidal anti-inflammatory drugs, sympathomimetic amines, ephedrine, glucocorticoids, cocaine and amphetamines can all cause significant hypertension.

Complications

The complications of hypertension can be considered either hypertensive or atherosclerotic. Although the extent of damage often correlates with the level of blood pressure, it is not always the case. Blood pressure and organ impairment should be evaluated separately. The various complications are as follows:

1. Hypertensive Heart Disease
   - Hypertension has the following effects on the heart: left ventricular hypertrophy, increased risk of coronary artery disease, arrhythmias, congestive cardiac failure and sudden death.[96]
   - Most episodes of left ventricular failure in hypertensive patients are associated with diastolic heart dysfunction.
   - Treatment of hypertension can reverse ventricular hypertrophy.[97,98] However, the impact of reduction of LVH on reduction of morbidity and mortality is still debated.
2. Cerebrovascular Disease
   - Hypertension is the most important modifiable risk factor for all types of atherothrombotic stroke[99] and intracerebral haemorrhage due to rupture of Charcot-Bouchard aneurysms.
   - The relation between the incidence of stroke and blood pressure is continuous.[100,101] A 5-6 mm Hg reduction in diastolic blood pressure reduces the risk of stroke by 40%.[102]
   - The SHEP (Systolic Hypertension Elderly Program) study showed substantial benefit following control of systolic blood pressure in the elderly.[36]
3. Kidney
   - About 20-25% of renal failure is attributed to uncontrolled hypertension.[103]
   - Development of renal damage is heralded by microalbuminuria, which progresses to overt proteinuria and may further progress to end-stage renal disease.[104]
   - Reduction of proteinuria can be achieved by effective blood pressure control specially with use of ACE inhibitors and ARBs.[105,106]
4. Retina
   - Hypertensive retinopathy is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure.
   - The classification of Keith, Wagener and Barker has been widely used. Grade I retinopathy is characterized by copper wire appearance; Grade II by arteriovenous nipping; Grade III by the presence of haemorrhages and exudates; and Grade IV by papilloedema.
   - Grade III and IV retinopathy is seen in long standing uncontrolled hypertension. These changes may regress with effective control of blood pressure.
   - Several reviews of hypertensive retinopathy since 1996 have questioned the usefulness of the classification system by Keith, *et al* and its relevance to current clinical practice. Recent studies show that some of the retinal signs (e.g., hemorrhages, microaneurysms and cotton-wool spots) predict stroke and death from stroke independently of elevated blood pressure and other risk factors.[107]
5. Large Vessel Disease
   - Hypertension is a risk factor for development of intermittent claudication. It also increases the risk of abdominal aortic aneurysms and aortic dissection. Eighty percent of patients with aortic dissection have hypertension.[108]
6. Hypertensive crises

   Hypertensive crises are classified as hypertensive emergencies or urgencies.

   Hypertensive emergencies:

   Hypertensive emergencies (Malignant Hypertension) 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) often with parenteral agents over a period of 6-8 hours with constant monitoring, 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 nitroglycerine is generally used although it is not very effective, but specially useful in patients with ischaemic heart disease and left ventricular failure.[109] The recommended dose is initially 5mcg/min, then titrate by 5mcg/min at 3 to 5 minute intervals, upto 10mcg/min. Intravenous enalaprilat is useful in hypertensive emergencies, specially in presence of heart failure. It is used in dosages of 0.625 – 1.25mg bolus every 6 hours. IV Labetalol is also being used in hypertensive emergencies in a bolus dosage of 2-10mg and infusion of 2.5-30 mcg/kg/min. IV esmolol has been shown to be specially useful for peri-operative accelerated hypertension. Usual bolus dose is 80-500 mcg/kg over 1 minute followed by an infusion of 50-300 mcg/kg/min. 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. The dose is 0.3mcg/kg/min to a maximum of 4mcg/kg/min. Sublingual captopril can also be used when less rapid reduction is required.

   Hypertensive urgencies:

   Hypertensive urgencies (Accelerated Hypertension) 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 with oral medication over a period of 1-3 days.[110] In most urgencies, blood pressure can be controlled with rapidly acting oral medications like calcium channel blockers and ACEI/ARB.

   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.[2,111]

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.[111] 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.[113]
- 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[27] and HOT[26] 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.[34]
- 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.[114]
- 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[169] and ARBs in the ONTARGET trial[163] 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.[37] The combination of amlodipine and perindopril was associated with significantly less incidence of new onset diabetes as compared to the combination of β-blocker and diuretic.
- β-blockers potentially mask hypoglycemic symptoms. β-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 β-blockers like nebivolol and carvedilol. α 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.[115]
- The ADVANCE trial[116] and INVEST trial[117] 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-psycological factors.
- The drugs which are useful in diabetic pregnant patients who are hypertensive include methyldopa, calcium channel blockers and labetolol. 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%.[2,28]
- 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.[2]
- 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.[118]
- 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.[12]
- In acute intracerebral hemorrhage, the SBP and DBP should be maintained below 180/105 mm Hg respectively.[106]
- 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.[119]
- 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.[33]

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.[2,120]
- 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.[2,121] 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.[122,123]
- 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.[124]
- 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.[125,126]
- 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.[127]
- Intravenous magnesium sulphate is the drug of choice both for prevention and treatment of seizures.[128,129] 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.[130] A community based study in Mumbai[131] 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.[132]

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.[133]

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.[134]

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).[44,135]
- 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.[136]
- 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.[124,137]

- 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 β-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, α 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 (HFnEF) is an entity which is being increasingly recognized now in elderly hypertensives who present with dyspnea. The prevalence of HFnEF 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 β-blockers and positive inotropes are not useful in these patients.[138,139]

- 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.[140]
- 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 β-blockers such as metoprolol, bisoprolol and α-β blocker carvedilol may be used wherever indicated. Use of these β-blockers has been shown to reduce mortality. These agents should be started in low doses and then gradually increased.[141-148]
- 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.[59] 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 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[149] including almost 12000 patients with systolic heart failure, and therefore at high risk of atrial fibrillation, β-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 β-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, β-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 recommended that if cough develops, angiotensin II receptor blockers should be tried as alternative to ACE inhibitors.
- β -blockers and α-β blockers are not routinely recommended as they are known to exacerbate asthma. However, α-blockers can be used as add-on therapy in patients with COPD.[150]
- 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.[133] Blood pressure levels have been shown to be positively and continuously related to the risk of major CAD events.[90]

- 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.
- β-blockers and CCBs are the drugs of first choice in the management of angina in patients with hypertension associated with CAD.
- β-blockers have been shown to reduce the risks of re-infarction and cardiovascular death by 25% in patients with MI.[150]
- Amlodipine has been shown to produce subjective and objective improvement in patients with angina.[152]
- Treatment with amlodipine is associated with fewer hospitalisations for unstable angina and revascularisations in patients with angiographically documented CAD.[153]
- Verapamil and diltiazem reduce risk of developing MI following non-Q-wave myocardial infarction.[154]
- After MI, therapy with ACE inhibitors prevents subsequent heart failure and reduces morbidity and mortality[155] ACE inhibitors in combination with digoxin or low dose diuretics, are effective in reducing morbidity and mortality in patients in heart failure.[156]
- Statins and aspirin are recommended in patients with hypertension associated with CAD.

Hypertension with Dyslipidaemia

Dyslipidaemia often co-exists with hypertension.[157]

- 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 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.
- β-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.[31,32,67,158]

Table 20 : Causes of resistant hypertension[2]

- 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

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.[159,160]

- Compared with Whites, Indian men and women have a higher prevalence of central obesity.[161] 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.[162] In Asians, the BMI cut-offs for overweight (>23.0 kg/m^2) and obesity (>25.0 kg/m^2) are lower than WHO criteria. These provisional recommendations will need to be revised in the light of further validation of studies and clinical experience.[150,163]
- 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.[164] 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.[165]
- 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.[166]
- On the basis of their favourable metabolic profiles, it would appear that ACE inhibitors, ARBs, CCBs and α-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. α -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.[154,167]

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 hypertenive 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.[168]

Table 20 gives causes of resistant HT[2]. 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.[76] However, long term follow-up will determine the utility of this therapy.

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