And when I am ill, it is he (Allah) who Cures me

Parah 19, Sorat-un-Assura’a, Ayat 80
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Pulse International, Karachi

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AKUH, Karachi
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PREFACE

Hypertension is a silent killer that affects 18% of the adult population in Pakistan (above the age of 18 years).

First National Guidelines on Hypertension were issued in 1998 by Pakistan Hypertension League. A lot of new and significant data has become available since that time which has helped to modify the approach towards the management of hypertension.

Thus in the light of new and continuously emerging data there has been a need to bring about new guidelines for the benefit of all concerned. Pakistan Hypertension League (PHL) assigned this task to its scientific committee and at the same time Pakistan Cardiac Society (PCS) through its Scientific Council on Hypertension assigned the responsibility to the first undersigned. Therefore, it was decided to form a collaborative group to come up with the draft of the guidelines through several deliberations, the collaborative group, along with the help of the advisors, has produced this document. We are indebted to them for their hard work.

Efforts have been made to incorporate the national habits and scenarios wherever possible in the light of the local data.

We sincerely hope that this document will meet the expectations of the profession at large and will be useful as a source of information to be used in practice on day to day clinical use.

Dr. Maqbool H. Jafary
Chairman, Scientific Committee, Pakistan Hypertension League
Chairman, Hypertension Council, Pakistan Cardiac Society
(maqbool.jafary@gmail.com)

Professor Mohammad Ishaq
President, Pakistan Hypertension League
(khyber50@yahoo.com)
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1. INTRODUCTION

1.1 Global Perspective

Hypertension is a worldwide disease. It is a major contributor of the cardiovascular disease. Increasingly common combination of being overweight or obese, diabetes, dyslipidemia and high blood pressure lead to morbidity and mortality through heart attacks, stroke, renal failure and dementia.

In 2000, the estimated number of adults with hypertension worldwide was 972 million out of which 639 million (65.7%) live in developing countries. By the year 2025, this number is likely to increase to 1.58 billion. Improper lifestyle factors like physical inactivity, salt and fat rich diet and increasing tobacco use especially in the developing countries are responsible for increased disease burden. Modern amenities of life with everything getting remote control is making the man inactive and this inactivity is inviting chronic diseases like hypertension and diabetes.

1.2 Pakistani Perspective

Hypertension is a global problem and the global burden of disease is more than that of coronary artery disease. There will be 1.5 billion hypertensive patients by 2025 Pakistan. According to the National Health Survey of Pakistan (NHSP) the projected figures, has shown around 12 million hypertensive patients, which also reflects the rampant course coronary artery disease has taken in the country. Unlike the United States and other developed economies, Pakistan is hit with a double burden of disease, that of infectious diseases and also of the non-communicable chronic diseases that include coronary artery disease and its risk factors. The young Pakistani population, which is at its most productive period, is hit at this very crucial juncture via economic productivity both individually and collectively as a nation. This loss of productivity is further compounded by the cost that goes towards treatment of hypertension and its complications. In Pakistan, over 90 percent payment for medical care is out of pocket, the concept of health insurance is inadequate and other means of re-imbursement are rudimentary. Therefore, we need to be cognizant of the implications of mismanaging a disease that can have catastrophic implications.

Hypertension is a disease which is very well studied and has the backing of robust clinical data. There is emerging local data also that may help us making decisions best suited to our community and ethnic population. In this regard, Jafar et al. studied the variations in hypertension within ethnic sub-groups in Pakistan. It was a cross-sectional survey (National Health Survey of Pakistan (NHSP) (1990-1994)), which included a total of 9442 individuals aged 15 years or over. Data on socio-demographics and clinical variables were collected. Distinct ethnic sub-groups - Muhajir, Punjabi, Sindhi, Pashtun and Baluchi - were defined by mother tongue. The age-standardized prevalence of hypertension was highest among Baluchis (25.3% in men and 41.4% in women), then Pashtuns (23.7% in men and 28.4% in women), Muhajirs (24.1% in men and 24.6% in women), and lowest among Punjabs (17.3% in men and 16.4% in women) and Sindhis (19.0% in men and 9.9% in women) (P = 0.001).

### HYPERTENSION IN DIFFERENT ETHNIC GROUPS IN PAKISTAN

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALUCHIS</td>
<td>25%</td>
<td>41%</td>
</tr>
<tr>
<td>PASHTUNS</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>MUHAJIRS</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>PUNJABIS</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>SINDHI</td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

Hypertension is the major risk factor for cardiovascular disease the world over. It afflicts 18% of the population above the age of 18 years in Pakistan. There are ethnic differences in the prevalence of the disease and in Baluchis the age-differentiated prevalence is highest at 26% in men and 41% in women while Sindhis have the lowest rates at 19% in men and 10% in women. Awareness of the disease is low and a significant number of patients present with complications like stroke and heart attacks as the first manifestation.

The diagnosis of hypertension needs to be made carefully keeping in mind that there are close to 20 variables the care of which determines the correct measurement of blood pressure. Not only the adults are vulnerable to the disease but also children can have high BP. There are percentile charts available for children to indicate the right BP in 2-17 years of age.

There is some variability in the classification of hypertension as per the authoritative bodies like JNC in USA, ESC/ESC in Europe and WHO. However, there is a consensus that the normal BP should be < 120/80 mmHg and BP above 140/90 is treatable. Evaluation of the patients requires a careful consideration of history, physical examination, laboratory and radiology support, and a keen eye to assess target organ damage and to rule out secondary hypertension. The data thus collected makes the basis for risk stratification of these patients and eventual management.

The management of these patients initially needs a focus on non-pharmacological measures. The DASH diet especially rich in vegetable and fruits and low in salt and fats is important. In our setting the amount of salt consumed is four times higher than the recommended 5-6 grams per day. Use of items like fish/fish oil, garlic and olive oil may have additional supplementary effect on lowering the blood pressure. Weight reduction through dietary means and exercise, avoidance of tobacco and alcohol and too much caffeine, relaxation techniques to reduce stress also help in reducing high BP.

Concurrent to non-drug management, pharmacological intervention is the mainstay in majority of the individuals. There is plethora of data to confirm the effectiveness of all the types of anti-hypertensives available today. However, based on the risk stratification, the selection of drugs can be made for the initial treatment. For uncomplicated hypertension with no or little target organ damage, any of the four major classes of drugs can be used but more recently beta-blockers have been de-emphasized due to their diabetogenic potential. Instead ACE-I/ARBs are preferred in patients 55 years are below while CCBs and diuretics are preferred in > 55 years, Asians and Chinese. Beta-blockers have a strong presence in hypertension complicated by CCF and CAD. Likewise ACE-I/ARBs have strong evidence in hypertension with diabetes, LV/LV Dysfunction and renal disease.

Diuretics, being very economic drugs may be used as a first line therapy in countries like Pakistan. However, CCF is a compelling indication for diuretics. CCBs have their forte in hypertension with CAD, isolated systolic hypertension and in the elderly. More often not, a combination of drugs from different classes has to be used for optimal control of BP.

While managing hypertension, certain special situations need to be kept in mind and these include children, diabetics, pregnancy, neurological disorders, metabolic syndrome etc. Clinicians need to be aware of special types of hypertension like white coat hypertension and masked hypertension. Apparently resistant hypertension is rare but requires a careful look at the potential causes.
While hypertension was more prevalent in urban (22.7%) versus rural dwellers (18.1%) (Odds ratio (OR) 1.34; 95% confidence interval (CI), 1.20, 1.49), this difference was no longer significant after adjusting for body mass and waist circumference (OR 1.03; 95% CI, 0.91, 1.16). However, ethnic differences persisted after adjusting for major socio-demographic, dietary and clinical risk factors. They concluded that although a threefold difference in prevalence of hypertension exists between people of South Asian descent which, unlike the urban/rural difference, cannot be accounted for by measured risk factors. In another study Siddiqui et al. conducted a cross sectional survey of a squatter settlement in Karachi. They found that according to the current staging of hypertension, 52.5% were normal, 40.4% were pre-hypertensives, 5.6% were stage I and 1.5% were stage II. Similarly for diastolic BP, 53% were normal, 32.8% were pre-hypertensives, 10.1% were stage I and 4% were stage II. The overall prevalence of hypertension in this study was 15% with 7.6% in males and 14% in females. Studies done in low socioeconomic areas of Punjab (Raza et al.) and Karachi (Malik et al.) showed a prevalence of 5% and 17% respectively. Another study done in a squatter settlement of Karachi revealed a prevalence of 26% with males (34%) and females (24%). Another study from Punjab showed that subjects having BMI >27 kg/m² had a higher prevalence of hypertension (48%) and a higher prevalence of hypertension in diabetics. In another study, Jafar et al., analyzed data for 8972 people aged 15 years or more from the National Health Survey of Pakistan (1990–1994). People considered overweight or obese were those with a BMI of 23 kg/m² or greater and those considered obese as having a BMI of 27 kg/m² or greater. They found that one in five of the population of Pakistan is overweight or obese with the use of Indo-Asian-specific BMI cutoff values. They recommend that optimal identification of those at risk of hypertension and diabetes and healthy targets may require the use of even lower BMI cutoff values than those already proposed for an Indo-Asian population. In the Metrowide Health study, which was in an urban setting, Dennis et al. sought to describe the distribution of overweight and obesity and their associated risk factors in India. They found that over 9% of the population has hypertension coexisting with overweight and obesity. Cardiovascular disease risk factors were prevalent in Metrowide and total cholesterol and waist circumference were significantly correlated with obesity measures. In another study, Jafar and colleagues studied the prevalence of coronary artery disease (CAD) and its risk factors in Karachi and demonstrated that one in four middle-aged adults had CAD. Risks are uniformly high in the young and in women. We therefore see from the above data that our population has risk factors as well as cardiovascular manifestations which are emerging in epidemic proportions and pose a public health threat.

After collecting figures which represent the diverse populations that we have and taking into the magnitude of the problem, we are further humbled by the fact that according to the NHSP less than 3 percent of the hypertensive patients are controlled, a figure that is dismal. We, therefore, need a new, specific approach, which is community based and has political will, which is vital for survival of any project. Analyzing the knowledge and attitude of general practitioners (GP) for their approach to hypertension in accordance with guidelines, Jafar et al., found that GPs in Pakistan under-diagnose and under-treat high BP, especially in the elderly. Their findings underscore the need for urgent revision of teaching curricula in medical schools with regard to the risks, complications, and management of hypertension, as well as the initiation of widespread and intensive continuing medical education for all physicians involved in the management of patients with hypertension. Particular efforts are needed to encourage the use of cost effective antihypertensive agents. In a similar study, Hameed et al. also found disturbing trends in that approximately 50% of the GPs taking part in a CME workshop on hypertension could not define hypertension and 75% believed that anxiolytics were first line therapy for hypertension.
1.3 Therapeutic Scenario

There is evidence that lowering BP to target range is beneficial. We have good and fairly safe drugs to do that. All drugs lower BP but some drugs have additional benefits. Some drugs have data to support use in certain co-morbid conditions like diabetes mellitus with hypertension and multiple studies have shown benefits for use of Angiotensin Converting Enzyme Inhibitors (ACEI). Similarly, some drugs have side effects and are not suited for certain populations like the use of diuretic therapy for the control of BP in the professional athlete, where it is relatively contraindicated. This is the time for combination therapy as we know that moderate doses of two drugs through their synergistic action help to control BP better than a maximum dose of a single drug. It also helps keep drug side effects minimal with use of doses in moderation. However, certain drugs do not work well in combination like beta-blockers and diuretic, where multiple studies have shown to increase the incidence of new onset diabetes by up to 32%. In view of the above local data it would seem prudent not to use beta-blocker and diuretic combination for uncomplicated newly diagnosed hypertension, as our population seems to be prone to develop central obesity and diabetes. Any approach that we adhere to today will have far reaching effects. In view of this emerging data, the same guidelines have made relevant changes to adjust for this. The National Institute of Health and Clinical Excellence (NICE) guidelines are the latest in this series. Those guidelines have relegated the role of beta-blockers to 4th line therapy for new cases of hypertension, who do not have any co-morbidities or any compelling indication. This major change has come about when meta-analyses showed that beta-blockers on their own were not reducing cardiovascular endpoints as was expected and other drugs, like the ACEI for example were doing this. It has also come to light that a level of sustained aerobic exercise, diet and weight loss are more important than the maximum dose of a single drug in their effect on BP lowering. The Government of Pakistan has realized the predicament of the population viz a viz hypertension and other non-communicable diseases and the National Action Program is a step forward to achieving the goal but a lot more coordinated effort is needed to make any significant difference.
2. DEFINITIONS

2.1 Hypertension:

Hypertension is defined as an average of two blood pressure readings of > 140 mm Hg systolic or > 90 mm Hg diastolic pressure taken after appropriate rest and under baseline conditions on two separate days. When average blood pressures are close to one of the dividing points for diagnosis, i.e., high normal pressures, there is a tendency for miscalculation. Attention needs to be paid to:
1. Correct cuff size
2. Accuracy of the manometer
3. Training and reliability of the observer
4. Sufficient number of measurements

2.2 Isolated Systolic Hypertension:

This is considered a special form, with an increase of the systolic value to > 140 mm Hg and a normal diastolic value (< 90 mm Hg).

2.3 Isolated Diastolic Hypertension:

This is defined as a systolic value of < 140 mm Hg, but a diastolic value of > 90 mm Hg.

2.4 Hypertension in the children:

In children aged up to 14 years, the defined limits are dependent on age in relation to height. Constantly measured systolic values of > 120 mm Hg in infants (first year of life, height less than 90 cm), > 130/80 mm Hg in small children (2-5 years, height 90-120 cm), > 130/85 mm Hg in schoolchildren (6-11 years, height 120-160 cm), and > 140/90 mm Hg in adolescents (height more than 150 cm) necessitate a diagnostic clarification. Adult values are applicable from age 14 years onward. Percentile chart below gives the absolute values of normal and high blood pressure based on age. (Figure 1)

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal BP</th>
<th>Hypertension</th>
<th>Severe Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Years</td>
<td>92 / 66</td>
<td>107 / 70</td>
<td>108 / 72</td>
</tr>
<tr>
<td>03-05 Years</td>
<td>104 / 68</td>
<td>109 / 71</td>
<td>120 / 84</td>
</tr>
<tr>
<td>06-09 Years</td>
<td>109 / 71</td>
<td>114 / 75</td>
<td>125 / 88</td>
</tr>
<tr>
<td>10-12 Years</td>
<td>116 / 76</td>
<td>120 / 79</td>
<td>133 / 90</td>
</tr>
<tr>
<td>13-15 Years</td>
<td>122 / 80</td>
<td>127 / 83</td>
<td>141 / 94</td>
</tr>
<tr>
<td>16-17 Years</td>
<td>129 / 81</td>
<td>134 / 88</td>
<td>147 / 103</td>
</tr>
</tbody>
</table>

Figure 1: Blood Pressure Percentile Chart in Children
1.4 Aims of Consensus Document

It is at this juncture that the Pakistan Hypertension League (PHL) and Pakistan Cardiac Society (PCS) felt the need for the current guidelines. The aim is to have a comprehensive document that would, in a simplified way, iron out the controversies in the light of the literature, tailor recommendations with regard to our societal and health needs and standardize the recommendations in order to have a country wide consensus on the management of hypertension. In order to achieve that, a nationally representative Collaborative Group of academicians was put together. The group met and brainstormed on issues in light of old and emerging literature and produced a document which was a document of consensus with good scientific content. As Hypertension cuts across many disciplines of medicine, an input from the experts in the respective disciplines was sought to make the document as comprehensive and representative as possible.

Hypertension remains one of the best studied disease entities at the dawn of 21st century and is backed by robust scientific evidence to help us deal with this menace. We can do this in a scientific, humanistic and economically viable manner. All documents are time limited and there is always room for improvement. PHL and PCS have made a concerted effort to make this document as the best reflected thoughts of our time on the subject. On its own, the document is nothing unless it is taken to the grass root level and the knowledge disseminated into practice which in turn will help us change practice patterns and bring more hypertensive cases to diagnosis and treatment. It is also very strongly felt and endorsed by the Group that hypertension management be added as a clinical module at the undergraduate level, as we have to change the thought process in the bud to be hopeful of seeing an effective change.

AIMS OF CONSENSUS DOCUMENT

- Collaborative efforts of PHL & PCS
- Comprehensive document to make recommendations for the management of hypertension in the country
- Involvement of experts in various disciplines of medicine dealing with hypertension
- Unify the process of diagnosis and management of a killer disease
BP measurements in different settings have generated different target values for the definition of hypertension. (Table 1)

1. Clinic BP: $\geq 140/90$ mmHg.
2. Home BP measurement: The values obtained from self-measurement by the patient are lower than clinical practice values, with hypertension defined as blood pressure $>135/85$ mm Hg.
3. Ambulatory BP measurement (ABPM): Mean 24-hour value $>130/80$ mm Hg, mean day value $>135/85$ mm Hg, mean night value $>120/70$ mm Hg.

<table>
<thead>
<tr>
<th>Table 1: BLOOD PRESSURE THRESHOLDS WITH DIFFERENT TIMINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Clinic</td>
</tr>
<tr>
<td>24 hour</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>Night</td>
</tr>
<tr>
<td>Home</td>
</tr>
</tbody>
</table>

2.5 Instruments:

All types of validated (by either of the European or American instrument validation bodies) and calibrated (regularly) aneroid, mercury or electronic apparatuses are acceptable.

2.6 Cuff sizes:

As the arm thickness increases as in obesity, so does the size for the appropriate cuff. For example, using a smaller cuff will give falsely elevated readings and vice versa. (Table 2 & 3)

<table>
<thead>
<tr>
<th>Table 2: APPROPRIATE CUFF SIZE (WHO Expert Committee)</th>
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<tbody>
<tr>
<td>Application</td>
</tr>
<tr>
<td>New born</td>
</tr>
<tr>
<td>Infant</td>
</tr>
<tr>
<td>Child</td>
</tr>
<tr>
<td>Adult</td>
</tr>
<tr>
<td>Large adult arm</td>
</tr>
<tr>
<td>Adult thigh</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: CORRECT CUFF SIZES BASED ON MID-ARM* CIRCUMFERENCES</th>
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</thead>
<tbody>
<tr>
<td>Arm Circumference (cm)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>$&lt; 33$</td>
</tr>
<tr>
<td>33 - 42</td>
</tr>
<tr>
<td>$&gt; 42$</td>
</tr>
</tbody>
</table>

(*Mid arm circumference is defined as half the distance from the acromion to the olecranon)

NICE 2004
3. MEASUREMENT OF BLOOD PRESSURE (BP)

3.1 Clinic Blood Pressure Measurement

It is still recommended to use a mercury sphygmomanometer. If another form of sphygmomanometer is used, it should be calibrated regularly against a mercury sphygmomanometer to ensure accuracy. Because of environmental concerns about the toxicity of mercury, there is a move to phase out mercury sphygmomanometers. At present there has been no agreement relating to an optimal replacement, as the accuracy of other available devices is dependent on the particular product chosen.29 The following variables need special attention:

1. The patient should be seated and relaxed, preferably for several minutes prior to the measurement and in a quiet room.
2. The arm being used for measurement should be free of constricting clothing so that the cuff can be wrapped around the upper arm without impediment.
3. Select an appropriate cuff size (see table of cuff sizes).
4. The bladder length should be at least 80% and the width at least 40% of the circumference of the mid-upper arm. Use of a ‘standard size’ cuff in people with large arms can result in artificially high blood pressure readings. If an oversized cuff cannot be satisfactorily fitted on a large arm then the utilization of an appropriately sized cuff on the forearm with radial artery auscultation should be considered.
5. Wrap the cuff snugly around the upper arm, with the centre of the bladder of the cuff positioned over the brachial artery and the lower border of the cuff about 2 cm above the bend of the elbow.
6. Ensure the cuff is at heart level by appropriately supporting the arm whatever the position of the patient.
7. Inflate the cuff to the pressure at which the radial pulse disappears.
8. Deflate the cuff at a rate of 2-3 mm Hg/beat or less and note the pressure at which the radial pulse reappears.
9. Fully deflate the cuff, wait approximately 30 seconds and then inflate the cuff to at least 30 mm Hg above that at which the radial pulse reappeared.
10. While deflating the cuff at a rate of 2-3 mm Hg/beat or less, auscultate over the brachial artery at the elbow.
11. Record the result for systolic and diastolic pressures to the nearest 2 mm Hg. For the systolic reading, record the level at which the first (at least two consecutive) sound is heard, even if they subsequently transiently disappear with progressive deflation (the ‘auscultatory gap’).

Practice Points
- Patients should sit for several minutes in a quiet and comfortable place.
- Take minimum 2 measurements at least 1-2 minutes apart.
- Use appropriate cuff size for age and weight.
- Have cuff at heart level.
- Measure Blood Pressure in both arms. Take the higher value as baseline.
- Measure BP in standing position in elderly, diabetes and in case of hypotension inducing drugs.
- Ask the patient to return for 1-2 more visits, if BP is elevated on first visit (to confirm the diagnosis of hypertension, before start of treatment).

Practice Points
- Healthcare professionals taking blood pressure measurements need adequate initial training and should have their performance reviewed periodically.
- Devices for measuring blood pressure must be properly validated, maintained and regularly recalibrated according to manufacturers' instructions.
12. For the diastolic reading, use phase V Korotkoff (disappearance of sound). Only use phase IV Korotkoff (muffling of sound) if sound continues towards zero.

13. Wait 30 seconds before repeating the procedure in the same arm. Average the readings. If the first two readings differ by more than 10 mm Hg systolic or 5 mm Hg diastolic or if the initial readings are high, take several readings after five minutes of quiet rest, until consecutive readings do not vary by greater than these amounts.

14. Ideally, patients should not take caffeine-containing beverages or smoke for at least two hours before blood pressure is measured, as both tend to produce acute increases in blood pressure (and particularly in combination).

15. Measure blood pressure in both arms at the first visit, particularly if there is evidence of peripheral vascular disease. A variation of up to 5 mm Hg in blood pressure between arms can be acceptable. Whenever there is a persistent difference between the two arms due to certain conditions (e.g., chronic aortic dissection, subclavian artery stenosis) all blood pressure recordings should be taken from the arm with the highest reading.

16. Measure sitting and standing blood pressures in patients who are elderly, or have diabetes, or where orthostatic hypotension might be suspected. Repeat measurement after at least two minutes standing.

17. In Pakistani setting, BP is quite often measured with shirt sleeve on rather than bare arm, especially in ladies. A recent Canadian Study indicates that there is no difference in BP reading if average thickness of sleeves is 4.3 mm or less. (Journal of Canadian Heart Association 2008; 178:585)

3.2 Ambulatory Blood Pressure Monitoring (ABPM):

This is a process by which an ambulatory BP apparatus is hooked on to the patient for a period of 24 hours and takes serial readings depending on the time interval set between each two readings. The readings can be between 50 and 100 in all. It should be made sure that at least 85% of the readings have been recorded for reporting. The readings can be divided into daytime and nighttime readings from the account maintained in a diary that is given to the patient. The means of the readings are noted and the maximum readings are also noted. Percentage of the readings in the hypertensive range is also noted. If despite a normal range mean, the percentage of elevated BP readings is more than 20 to 30% then this is taken as significant. During night time BP normally settles to below 120/80 mmHg. This phenomenon is called the "nocturnal dip". Loss of nocturnal dip has also been noted in early hypertensive cases and is associated with end organ damage. Potential Indications for ABPM are given in Table 4.

**Table 4: POTENTIAL INDICATIONS FOR THE USE OF AMBULATORY BP MONITORING**

- Unusual BP variability
- "White Coat" hypertension
- Evaluation of nocturnal hypertension
- Evaluation of drug resistant or refractory hypertension
- Determining the efficacy of drug treatment over 24 hours
- Diagnosis and treatment of hypertension in pregnancy
- Evaluation of symptomatic hypotension
emphasized that the term mild hypertension does not imply a uniformly benign prognosis. The possibility of a "dual response" to known and unknown stressors needs to be evaluated. The initial response of the vascular bed could be 'reactive' with reversible changes and the later response could be structural and irreversible. 52, 53 During the reversible stage, hypertension could be easily controlled irrespective of the numerical value of BP whereas in the latter stages, it could become more difficult to control. More importantly, it will make the physician control the BP adequately and at the same time avoid unnecessary treatment. Therefore, we strongly recommend that this multi-pronged approach be adopted rather than just use numerical values.

5. SCREENING AND DETECTION

It is recommended that all subjects 18 years or above should be screened for hypertension. It is also suggested because it is for prevention and early detection of risk factors and because all the cardiovascular risk factors are prevalent in our country, that screening for diabetes and dyslipidemia may be carried out at the same time. This will help us address this in an integrated manner. The detection of hypertension would require:

- BP measurement in each subject who visits the doctor, regardless of the reason of visit
- Conduct of health surveys and observance of hypertension days
- Casual BP readings to be repeated from time to time

6. EVALUATION OF INDIVIDUALS WITH HYPERTENSION

6.1 Clinical and Family History:

Hypertension is a silent disease. It manifests, generally, as a complication of the target organs. Rarely people experience non-specific symptoms like headache, palpitation, sweating, dizziness etc., but by and large, most people are asymptomatic even with severely uncontrolled levels. A detailed case history about prior high blood pressure, renal disorders, stroke, heart attack, diabetes mellitus, complications during pregnancy, duration of high blood pressure, prior blood pressure crises, alcohol intake, drug history including NSAIDs, use of oral contraceptives, history of hypertensive drugs prescribed to date, success of therapy; any side-effects experienced with drugs, smoking habits and stress-prone personality. A family history of coronary artery disease, diabetes and hypertension is also essential.

Practice Points:
- Measure BP of each subject presenting in any clinic regardless of doctor specialty.
- If BP is normal, recommend that BP should be measured at least once a year.
- If BP values are borderline, BP should be checked more frequently (6 months) during the year.

Practice Points:
- Detailed history is essential.
- Prior history of high BP.
- Kidney disorders, stroke, heart disease, diabetes, dyslipidemia.
- Complications of pregnancy.
- Drug history:
  - NSAIDs
  - Oral Contraceptives
  - Previous antihypertensives.
- Family history of hypertension, heart disease, diabetes.
- Smoking and dietary habits
4. CLASSIFICATION OF HYPERTENSION

We have ascribed to the classification of hypertension as put forward by the JNC 7, because by creating a new class of high normal BP called pre-hypertension, it has helped categorize patients who are at a higher risk for adverse outcomes as compared to the normal level BP population. The other difference is that stages 2 and 3 of the JNC 6 have been amalgamated and as a result, only mild and severe categories remain. This makes the classification simple and user friendly.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines categorize hypertension as follows: (Table 5)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 and</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-Hypertension</td>
<td>120-139 or</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 - Hypertension</td>
<td>140-159 or</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 - Hypertension</td>
<td>&gt;=160 or</td>
<td>&gt;=100</td>
</tr>
</tbody>
</table>

European Society of Hypertension (ESH) / European Society of Cardiology (ESC) Guidelines, issued in 2007, have retained the classification of Hypertension of ESH / ESC Guidelines of 2003, which is as follows: (Table 6)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120 and</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129 and/or</td>
<td>80-84</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139 and/or</td>
<td>85-89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140-159 and/or</td>
<td>90-99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160-179 and/or</td>
<td>100-109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>&gt;=180 and/or</td>
<td>&gt;=110</td>
</tr>
<tr>
<td>Isolated systolic</td>
<td>&gt;=140</td>
<td>&gt;=90</td>
</tr>
</tbody>
</table>

Classifying hypertension is not a simple matter and we need to remember that just giving numbers can help us but the categorization process will require much more i.e., taking into account the possibility of target organ damage, risk factor profile and the level of resistance that may be faced in the medical treatment of BP levels. Blood pressure (BP) is a biological variable and an absolute values cannot be determined. There is a wide variability in the BP readings of the same individual.

For example a hypothetical case with initial BP of 170/100 mmHg without risk factors or complications, controlled with one drug will be described as "mild hypertension controlled to a target of 120/80 mmHg" if the "normal BP" is defined as 120/80 mmHg. This example highlights the fact that when we classify hypertension, we should be looking at:

1. What is the absolute BP reading?
2. Whether there is a complication i.e., target organ involvement.
3. Risk factor profile i.e., diabetes mellitus, smoking, dyslipidemia etc.

The advantages of this system are many. The classification provides an easy qualitative assessment of the disease. Sometimes, the so-called stage 1 could be more resistant to treatment and the so-called stage 2 could be more easily controlled. This fact has been alluded to in the WHO-ISH 1999 guidelines (8) which state, "It is
Table 7: PHYSICAL EXAMINATION

Full physical examination with particular attention to:
Presence of other cardiovascular risk factors;
Body size is assessed and monitored by measuring:
  - **Waist circumference**: measured half way between the inferior margin of the last rib and the crest of the ilium in the mid-axillary plane. The measurement is taken at the end of normal expiration. Increased risk is > 35.5 inches in males and > 31.5 inches in females and/or
  - **Body mass index (BMI)**: body weight in kilograms divided by the square of height in meters (kg/m²). Overweight: BMI ≥ 23 kg/m², Obesity: BMI ≥ 27 kg/m² (Indo-Asian Values)

Table 8: PHYSICAL EXAMINATION FOR SECONDARY HYPERTENSION & TARGET ORGAN DAMAGE

- Features of Cushing syndrome
- Skin stigmata of neurofibromatosis (pheochromocytoma)
- Palpation of enlarged kidneys (polycystic kidney)
- Auscultation of abdominal murmurs (renovascular hypertension)
- Auscultation of precordial or chest murmurs (aortic coartation or aortic disease)
- Diminished and delayed femoral and reduced femoral blood pressure (aortic coartation, aortic disease)

Cardiovascular system:
1. Heart size
2. Evidence of heart failure
3. Evidence of arterial disease – carotid, peripheral, renal
4. Absent femoral pulses or radio femoral delay

Lungs:
1. Basal crepitations
2. Wheeze

Abdomen:
1. Renal size
2. Other masses
3. Bruits

Eyes:
1. Haemorrhages
2. Exudates
3. Status of blood vessels

Brain:
1. Murmurs over carotids
2. Motor or Sensory Deficits
Table 9: SIGNS OF ORGAN DAMAGE

- Brain: murmurs over neck arteries, motor or sensory defects
- Retina: fundoscopic abnormalities
- Heart: location and characteristics of apical impulse, abnormal cardiac rhythms, ventricular gallop, pulmonary rales, dependent edema
- Peripheral arteries: absence, reduction, or asymmetry

This baseline information is important in placing the patient into our treatment plan. It is imperative that the target organs like the eyes, heart, brain, kidney and peripheral vessels be assessed on physical exam and with further investigations, in order to stage the severity of the organs involved and risk stratify the patient for further treatment. This risk is reflected in the WHO classification of target organ damage Stages I to III (Table 10).

<table>
<thead>
<tr>
<th>Stage I</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>Left ventricular hypertrophy, benign retinopathy (constriction and sclerosis of retinal arterioles)</td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
</tr>
<tr>
<td>1 Cardiac: hypertensive heart disease, heart failure and coronary artery disease, myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>2 Cerebral: hypertensive encephalopathy, cerebral hemorrhage and stroke</td>
<td></td>
</tr>
<tr>
<td>3 Vascular: aortic aneurysm and peripheral artery disease (PAD)</td>
<td></td>
</tr>
<tr>
<td>4 Renal: renal failure</td>
<td></td>
</tr>
<tr>
<td>5 Ophthalmologic: malignant retinopathy (exudates, hemorrhages, retinal edema, papilledema)</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: EVALUATION OF TARGET ORGAN DAMAGE

- Eyes: Fundoscopy for retinal changes, hemorrhages, exudates and papilledema etc
- Brain: Infarct or hemorrhage; CT/MRI brain
- Heart: ECG, Echocardiogram, Angiogram
- Renal: Urine detailed report - microalbuminuria, biochemistry, US scan

6.3 Investigations:

Hypertension is 95% of the times, essential i.e., without an identifiable cause. The rest 5% is due to treatable causes and is referred to as secondary hypertension. While investigating we have to be cost effective.

Minimal investigations are given in Table 11:

Table 11: INVESTIGATIONS (MINIMAL)

- Urine analysis for proteins (can be done with a dipstick as a starter)
- Serum creatinine levels
- Serum potassium and sodium levels
- Random blood sugar
- ECG for evidence of established coronary artery disease (CAD) or LVH
- Chest X Ray PA view
Special Investigations:

For a more general assessment and especially when complications set in and to help in the tailoring of treatment options, the following tests may be added: (Table 12)

1. Complete blood count
2. Lipid profile
3. Echocardiogram
4. Specific tests (on case to case basis, depending on high suspicion of secondary hypertension): VMA/metanephrines, ultrasound scan of abdomen, Doppler Ultrasonography, IVU, Tc99 DTPA scintigraphy, renal angiogram, and CT/MRI.

Table 12: SPECIAL INVESTIGATIONS (On case to case basis)

- Echocardiogram
- Carotid (and femoral) ultrasound
- C-reactive protein
- Microalbuminuria (essential test in diabetics)
- Quantitative proteinuria (if dipstick test positive)
- Search for secondary hypertension: measurement of renin, aldosterone, corticosteroids, catecholamines, arteriography, renal & adrenal ultrasound, computer assisted tomography (CAT), magnetic resonance imaging
7. MANAGEMENT OF PATIENTS WITH HYPERTENSION:

Treating BP to target of less than 140/90 mm Hg is associated with a decrease in the cardiovascular complications. In patients with diabetes and chronic renal failure, the targets are more stringent with acceptable BP goal of less than 130/80 mm Hg. Most people will have their diastolic BPs reach goal once the systolic BP is controlled. Therefore, it is advisable to primarily treat systolic BP.

7.1 Risk Stratification (Figure 2)
7.2 Non-Pharmacologic Management:

If the incidence of hypertension in the population could be reduced through lifestyle modifications, much of the morbidity and mortality associated with coronary heart disease, renal disease and stroke might be prevented.\(^5\)

It has been proven beyond doubt that the non-pharmacologic changes that include lifestyle modifications and risk factor control combined, bring down the BP level more significantly than the maximum dose of a single antihypertensive drug.\(^6\) These can be addressed by paying particular attention to the 'SNAP' (Smoking, Nutrition, Alcohol, Physical Activity) risk factors.\(^6\)

7.2.1 Diet:

The Dietary Approaches to Stop Hypertension (DASH) trial showed overall reductions in BP of 11.4/5.5 mm Hg in hypertensive persons on a diet rich in fruits, vegetables and low-fat dairy products compared with control subjects.\(^7\) The DASH "combination diet" also produced reductions in BP of 3.5/2.1 mm Hg in subjects without hypertension. Remarkably, subgroup analysis of the DASH trial indicated that the combination diet lowered BP effectively in all participating groups examined, independent of race, sex, age, BMI, level of education, income, physical activity, family history of hypertension, and geographic location.\(^8\) Recommendations for the general public or the hypertensive patients are 4 servings of fruit, 4 servings of vegetables and 3 servings of low-fat dairy products per day. The paradigm shift toward recognition of the powerful role of total diet (rather than individual nutrients) in the prevention and treatment of hypertension in particular and CVD in general deserves emphasis.\(^9\)

**DAILY NUTRIENT GOALS USED IN THE DASH STUDIES**
(For a 2,100 Calorie Eating Plan)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Percentage of Calories</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fat</td>
<td>27%</td>
<td>65 g</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>6%</td>
<td>20 g</td>
</tr>
<tr>
<td>Protein</td>
<td>18%</td>
<td>45 g</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>55%</td>
<td>230 g</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>15%</td>
<td>350 mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>2,300 mg(^*)</td>
<td>2,300 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>1,250 mg(^*)</td>
<td>1,250 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>500 mg(^*)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>4,700 mg(^*)</td>
<td>4,700 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>30 g</td>
<td>30 g</td>
</tr>
</tbody>
</table>

\(^*\)1,500 mg sodium was a lower goal tested and found to be even better for lowering blood pressure. It was particularly effective for middle-aged and older individuals. African Americans and those who already had high blood pressure.

\(g = \text{grams}; \ mg = \text{milligrams}\)
cardiovascular diseases. Studies point to the fact that garlic reduces cholesterol, inhibits platelet aggregation, reduces blood pressure and increases oxidative status and the reduction in BP is partially mediated through reduction in intracellular sodium and ACE activity.

The evidence for the medicinal use of fruits and vegetables in general and some dietary supplements in particular is accumulating with rapid pace. Some of the individual dietary supplements as mentioned above have been shown to possess mild antihypertensive effect with expected synergism when used in combinations; hence their use either alone or in combination can be encouraged which may be curative in mild hypertension but more importantly they have the potential of having a drug sparing effect, which may help in reducing the side-effects, in addition to their other potential health benefits.

7.2.3 Weight reduction and maintenance of normal weight:

Weight loss is the most effective of all non-pharmacological measures to prevent and treat hypertension. This effect is independent of sodium restriction and is seen in both obese and non-obese hypertensive individuals. Clinical trial evidence suggests that weight loss interventions produce BP benefits that persist even after cessation of active therapy. Body mass index (BMI) should be maintained between 18.5 and 23 kg/m². Because sustained weight reduction is extremely difficult to achieve, emphasis should be placed on prevention of weight gain, particularly in younger individuals with pre-hypertension and in families with a high prevalence of hypertension.

7.2.4 Salt intake:

High sodium intake has generally been related to BP elevation, particularly in hypertensive individuals, and this effect appears to be augmented by concomitant low potassium intake. When sodium restriction was added to the DASH diet in the DASH-sodium trial, the reduction in sodium intake from the high (150 mmol/d) to the intermediate (100 mmol/d) level reduced SBP by 2.1 mm Hg when participants were on a usual diet and by 1.3 mm Hg on the DASH diet. Reducing the sodium intake from the intermediate to the low (50 mmol/d) level caused additional reductions of 4.6 mm Hg on the usual diet and 1.7 mm Hg on the DASH diet. The largest BP effect was observed with the combination of DASH diet and low sodium intake, although the effects were not fully additive. On the basis of these observations and the small but consistent BP-lowering effects observed in other clinical trials of dietary sodium reduction in hypertensive subjects (particularly those who are obese, elderly, black and/or female), avoidance of excessive sodium intake is recommended for hypertensive persons. Additional benefits of sodium reduction include reduced diuretic-induced hypokalemia, greater ease of BP control with diuretic therapy, protection from osteoporosis and fractures by reducing urinary calcium excretion and favorable effects on left ventricular hypertrophy. Therefore, we recommend a reduction in daily consumption of sodium chloride to 6 g and of sodium to 2.4 g. This can be achieved by avoiding obviously salty foods, not adding salt at the table and eating more meals cooked from natural ingredients. Whether this level of sodium reduction is helpful for the general population in preventing hypertension and related CVD morbidity and mortality is a matter of debate, considering the minimal effect of dietary sodium reduction on BP in normotensive subjects and possible adverse effects of reduced sodium intake on the cardiovascular system over time.

7.2.5 Exercise:

At least 30 minutes of moderately intense physical activity, such as brisk walking, swimming, bicycling or yard work, carried out at least 3 times per week (preferably once per day) can lower BP in both normotensive and hypertensive individuals. Studies suggest that such moderate activity may lower systolic BP (SBP) by 4 to 9 mm Hg. Additional benefits of regular physical activity include weight loss, enhanced sense of well-being, improved functional health status and reduced risk of cardiovascular disease (CVD) and mortality from all causes. Accordingly, regular aerobic physical activity is recommended for all persons, but those with advanced or unstable CVD may require a medical evaluation before initiation of exercise or a medically supervised exercise program. Isometric exercise such as heavy weight lifting can have a pressor effect and should be avoided. Due to cultural and social conditions, it is at times
difficult for women in Pakistan to exercise outside their homes. We, therefore, recommend the use of inhouse exercise equipment like treadmill or exercise cycle or the use of whatever space is available inside the house for walk etc. Use of stairs and avoidance of lifts is advisable. Table 15 gives details of calories used with various activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>150 - 200 lbs weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shopping</td>
<td>150 - 225</td>
</tr>
<tr>
<td>House work</td>
<td>150 - 190</td>
</tr>
<tr>
<td>Gardening</td>
<td>130 - 240</td>
</tr>
<tr>
<td>Golf</td>
<td>140 - 260</td>
</tr>
<tr>
<td>Swimming</td>
<td>360 - 490</td>
</tr>
<tr>
<td>Walking Brisk</td>
<td>450</td>
</tr>
</tbody>
</table>

Table 15: Calories consumed with a variety of activities

7.2.6 Alcohol use:

The use of alcohol is not a major problem in Pakistan. Alcohol consumption elevates BP both acutely and chronically. Cross-sectional and prospective studies involving all kinds of populations have demonstrated a consistent positive relationship between alcohol consumption, BP levels and the prevalence of hypertension. Excessive alcohol intake also appears to cause resistance to antihypertensive therapy. Clinical studies show that SBP falls by 2 to 4 mm with reduction in alcohol intake. For unrelated health and religious reasons, alcohol consumption is not recommended for nondrinkers; however, for those who are already drinkers, intake should be limited to 1 oz of alcohol per day for men and half that amount for women, while in the meantime efforts should be made to help quit alcohol as a therapeutic measure.

7.2.7 Tobacco use:

Cigarette smoking is a powerful risk factor for cardiovascular disease, and avoidance of tobacco in any form is essential. A significant rise in blood pressure accompanies the smoking of each cigarette. Those who continue to smoke may not receive the full degree of protection against cardiovascular disease from antihypertensive therapy. The cardiovascular benefits of discontinuing tobacco use can be seen within a year in all age groups. Smokers must be told repeatedly to stop smoking. The lower amounts of nicotine contained in smoking cessation aids usually will not raise blood pressure; therefore, these may be used with appropriate counseling and behavior interventions. Actions to avoid or minimize weight gain after quitting smoking are often needed. Smoking of sheesha, especially amongst the younger generation is becoming a fashion and it has acquired an epidemic proportion. As a part of an overall awareness campaign against tobacco use, sheesha use also needs to be discouraged.

7.2.8 Caffeine:

Caffeine may raise blood pressure acutely. Tolerance to this pressure effect develops rapidly and no direct relationship between caffeine intake and elevated blood pressure has been found in most epidemiologic surveys.

7.2.9 Stress:

Emotional stress can raise blood pressure acutely. The role of stress management techniques in treating patients with elevated blood pressure is uncertain. Relaxation therapies and biofeedback have been studied in multiple controlled trials with little effect beyond that seen in the control groups. The available literature does not support the use of relaxation therapies for definitive therapy or prevention of hypertension. One study found no effect of stress management on prevention of hypertension.
7.3 Pharmaceutical Intervention:

There is robust data available that proves the value of different classes of drugs such as Angiotensin Converting Enzyme inhibitors (ACEI), Angiotensin Receptor Blockers (ARB), Calcium Channel Blockers (CCB), Beta-blockers (BB) and thiazide/thiazide type diuretics (TD). Nonetheless, the JNC 7 has preferred diuretics as first line therapy, the other guidelines have kept the option open for all the above mentioned drugs. The recommended strategy is to favor a therapy that would confer on the patient an evidence based benefit. Most evidence of pharmacologic therapy comes from an older population, mean being 60 years. There is significant data in this age group for TD and CCB, as the mechanism of hypertension is thought to be a "low renin, volume dependent state". Whereas, the later day trials with younger population (less than 55 years) have been conducted with ACEI and ARBs with good effect, as the mechanism is "high renin state".

The Blood Pressure Lowering Trialists' Collaboration has conducted two major meta-analyses of blood pressure lowering drugs. The first compared the effectiveness of "newer therapies," such as treatments based on ACEI or CCBs, with conventional therapies (based on diuretics or beta-blockers) and concluded, while conceding that insufficient data existed, that newer therapies were as effective as older ones, but no more effective than, conventional therapy at reducing stroke, morbidity or mortality due to coronary heart disease or all cause mortality. The second meta-analysis included 29 major trials published as of 2003, with over 700,000 years of patient follow up. The findings of this second meta-analysis are largely consistent with the first: the main driver of benefit from blood pressure lowering therapy is blood pressure lowering per se, and little evidence exists of additional benefits specific to a class of drug with regard to major cardiovascular outcomes overall. The theory underpinning the AB/CD algorithm is that hypertension can be broadly classified as "high renin" or "low renin" and is therefore best treated initially with one of two categories of antihypertensive drug—those that inhibit the renin-angiotensin system (angiotensin converting enzyme inhibitors or angiotensin receptor blockers (A) or beta-blockers (B) and those that do not (calcium channel blockers (C) or diuretics (D))). People who are younger than 55 and white tend to have higher renin concentrations than people aged 55 or older or the black population (of African descent). A or B drugs are therefore generally more effective as initial blood pressure lowering treatment in younger white patients than C or D drugs. However, C or D drugs are more effective first line agents for older white people or black people of any age.

NICE Chart of AB/CD with de-emphasis on beta-blockers

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>&lt; 55 years</th>
<th>STEP 2</th>
<th>A+C or A+D</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP 3</td>
<td>A+D</td>
<td>STEP 4</td>
<td>Add: Further D/C therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alpha Blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beta Blockers etc</td>
</tr>
</tbody>
</table>

As regards the use of beta-blockers as first line therapy for uncomplicated hypertension without any compelling indications, like CAD, CHF etc., data and meta-analyses have shown that there is no clear and present role in primary prevention of cardiovascular disease, cardiovascular or all cause mortality. Additionally, there is increasing evidence that the most frequently used beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes. Therefore in the current NICE hypertension guidelines the role of beta blockers has been relegated to 4th line therapy for uncomplicated hypertension. However, BBs remain a first line therapy in hypertension with appropriate compelling indication.
Direct Renin Inhibitor (Aliskiren) has become available. Its comparative merits in clinical practice are being assessed.

Table 16: Selected Anti-hypertensives in various therapeutic groups, along with dosage and frequency

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasix</td>
<td>Sanofi</td>
<td>Furosemide</td>
<td>40 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td>Aventis</td>
<td></td>
<td>20 mg</td>
<td>BD</td>
</tr>
<tr>
<td>Lasoride</td>
<td>Sanofi</td>
<td>Furosemide +</td>
<td>40 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td>Aventis</td>
<td>Amiloride HCL</td>
<td>5 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Dyazide</td>
<td>GSK</td>
<td>Triamterene</td>
<td>90 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zafra</td>
<td>Hydrochlorothiazide</td>
<td>12.5 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BETA BLOCKERS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenormin</td>
<td>ICI</td>
<td>Atenolol</td>
<td>50 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Normitab</td>
<td>Nabiqasim</td>
<td>Atenolol</td>
<td>60 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Mesprin</td>
<td>Novartis</td>
<td>Metoprolol</td>
<td>50-100 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Concor</td>
<td>Merck</td>
<td>Bisoprolol</td>
<td>5-10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Puloc</td>
<td>Werrick</td>
<td>Atenolol</td>
<td>50 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Zanfot</td>
<td>Zafra</td>
<td>Atenolol</td>
<td>50 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE INHIBITORS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardace</td>
<td>Zafra</td>
<td>Enalapril</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Cardetec</td>
<td>Wilson</td>
<td>Enalapril</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Cortec</td>
<td>Nabiqasim</td>
<td>Enalapril</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Zestril</td>
<td>ICI</td>
<td>Lisinopril</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Lisipril</td>
<td>Werrick</td>
<td>Lisinopril</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Capoten</td>
<td>BMS</td>
<td>Captopril</td>
<td>25 mg</td>
<td>BID</td>
</tr>
<tr>
<td>Tritace</td>
<td>Sanofi</td>
<td>Ramipril</td>
<td>2.5 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td>Aventis</td>
<td></td>
<td>5 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CALCIUM CHANNEL BLOCKERS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norvasc</td>
<td>Pfizer</td>
<td>Amlodipine</td>
<td>5 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Sofvasc</td>
<td>Wilson</td>
<td>Amlodipine</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Lodopin</td>
<td>Merck</td>
<td>Amlodipine</td>
<td>5 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Cardiovasc</td>
<td>Werrick</td>
<td>Amlodipine</td>
<td>5 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Cardal</td>
<td>Abbott</td>
<td>Diltiazem</td>
<td>60 mg</td>
<td>TDS</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Bayer</td>
<td>Nitrdipine</td>
<td>60 mg</td>
<td>TDS</td>
</tr>
<tr>
<td>Calan</td>
<td>Searle</td>
<td>Verapamil</td>
<td>240 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VASODILATORS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apresoline</td>
<td>Alliance</td>
<td>Hydralazine</td>
<td>25 mg</td>
<td>TID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CENTRAL ALPHA AGONISTS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldomet</td>
<td>MSD</td>
<td>Methyldopli</td>
<td>250 mg</td>
<td>BID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALPHA ADRENOCEPTOR BLOCKING DRUGS</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardura</td>
<td>Pfizer</td>
<td>Doxazosin</td>
<td>2 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANGIOTENSIN II RECEPTOR ANTAGONIST</th>
<th>COMPANY</th>
<th>GENERIC</th>
<th>DOSE</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cozar</td>
<td>MSD</td>
<td>Losartan</td>
<td>50 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Diwan</td>
<td>Novartis</td>
<td>Valsartan</td>
<td>100 mg</td>
<td>OD</td>
</tr>
<tr>
<td>Advant</td>
<td>Getz</td>
<td>Candesartan</td>
<td>8 mg</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cilexetil</td>
<td>16 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>
Table 17: COMPELLING INDICATIONS

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Definite Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Elderly including ISH, CHF</td>
<td>Pregnancy, Gout</td>
<td>Low K+, Gout, Glucose intolerance</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>CCF, LV Dysfunction, Type 2 DM with nephropathy, Post – MI, IHD, Previous Stroke</td>
<td>Pregnancy, Renal artery stenosis</td>
<td>Cough, allergy, renal impairment, K+</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td>Intolerance to ACEIs, LVH, CHF, Type 2 DM, Microalbuminuria</td>
<td>Pregnancy, Renal artery stenosis</td>
<td>Raised K+ Hypotension, allergies</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>Symptomatic angina, Post MI, CCF with increased sympathetic drive, tachycardia</td>
<td>Asthma, COPD, PVD, AV Block</td>
<td>Fatigue, Wheeze, impotence</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Elderly, ISH, IHD</td>
<td>Heart Block, (Non-DPH CCBs)</td>
<td>Flushing, Ankle edema, headache</td>
</tr>
<tr>
<td>Alpha Blockers</td>
<td>Prostalism</td>
<td>Urinary Incontinence</td>
<td>Urinary Incontinence</td>
</tr>
</tbody>
</table>

CHF = Congestive Heart Failure, ISH = Isolated Systolic Hypertension, IHD = Ischemic Heart Disease, LVH = Left Ventricular Hypertrophy.

Table 18 gives the list of various clinical conditions which may co-exist with hypertension, along with preferred drug therapy.

Table 18: CONDITIONS FAVOURING THE USE OF SOME ANTI-HYPERTENSIVES VERSUS OTHERS

<table>
<thead>
<tr>
<th>Subclinical Organ Damage</th>
<th>ACEI, CCB, ARB</th>
<th>ACEI, ARB</th>
<th>ACEI, ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Event

<table>
<thead>
<tr>
<th>Previous Stroke</th>
<th>Previous MI</th>
<th>Angina Pectoris</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atrial Fibrillation

<table>
<thead>
<tr>
<th>Recurrent</th>
<th>Permanent</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESRD / Proteinuria

<table>
<thead>
<tr>
<th>Diuretics, BB, ACEI, ARB, Aldosterone Antagonists</th>
<th>ARB, ACEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB, Non-dihydropyridine CCB</td>
<td>BB, ACEI</td>
</tr>
<tr>
<td>ACEI, ARB, Loop Diuretics</td>
<td>BB, ACEI</td>
</tr>
<tr>
<td>CCB</td>
<td>BB, ACEI</td>
</tr>
</tbody>
</table>

Peripheral Artery Disease

<table>
<thead>
<tr>
<th>ACEI, ARB</th>
<th>CCB</th>
<th>ACEI, ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LV Dysfunction

<table>
<thead>
<tr>
<th>ISH in elderly</th>
<th>Metabolic Syndrome</th>
<th>Diabetes Mellitus</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liver Dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
</tbody>
</table>

 Variables Conditions

<table>
<thead>
<tr>
<th>Diuretic, CCB, ACEI</th>
<th>ACEI, ARB, CCB</th>
<th>ACEI, ARB, CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI, ARB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methyldopa, CCB, BB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BB</td>
<td></td>
</tr>
</tbody>
</table>

Any except Methyldopa

Any except Diuretics

CCB, ACEI, ARB

ACEI = Angiotensin Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker; BB = Beta Blocker; MI = Myocardial Infarction; Dav = Diabetic Nephropathy; ISH = Isolated Systolic Hypertension.
8. **HYPERTENSION IN SPECIAL SITUATIONS:**

There are groups where recommendations differ from the mainstream recommendations, due to an underlying primary disorder or type of population being treated.

8.1 **Children:**

In children and adolescents, hypertension is defined as elevated BP that persists on repeated measurement at the 95th percentile or greater for age, height, and gender. As with adults, the fifth Korotkoff sound is used to define DBP. In children secondary causes of hypertension should be ruled out. The hypertensive child should be recommended non-pharmacologic measures. Once these measured fail, then the drug therapy is the same as for the adults; only doses are smaller than the adult dose. It should, however, be noted that girls in the child bearing age are not prescribed ACEI or ARB because they are teratogenic.

In uncomplicated hypertension the children should be allowed to take part in normal activities.

---

**Figure 4: Management of Primary Hypertension in Children**

Note:
Algorithm after excluding secondary causes of hypertension

P = Percentile, C.C. = Continued Care,
LSM = Lito Systol modification, HTN = Hypertension, WI = Weight,
RPT = Repeat, TOD = Target Organ Damage
7.3.3 Evidence based combinations:

There is evidence for the use of ACEI/D, ARB/D, and ACEI/CCB. These combinations are commercially available. ACEI and BB are not considered a good combination, as both work through the renin mechanism. ACEI produces more renin, which helps it further in inhibition but this is possibly blunted by the BB. CCB of the non-dihydropyridine group such as verapamil is discouraged to be combined with BB due to the negative inotropic and chronotropic effect. The CCBs of dihydropyridine class cause peripheral edema which responds better to ACEI than diuretics, as it is produced not due to salt and water retention but due to capillary hypertension secondary to diminished arteriolar vasoconstriction in the upright posture. CCB and D combination works but there are no well controlled studies in this regard. In the setting of microalbuminuria, ACEI/ARB combination has shown some benefit in the CALM study but this is not recommended otherwise, except in cases of CHF, with some evidence of further reduction of morbidity and mortality. While using fixed dose combinations, one needs to be careful of the side effect profile of the ingredients. The patient needs to be educated and care should be taken to make adjustments with changes in volume and hemodynamics.
8.2 Pregnancy

Hypertension affects a significant number of pregnant women in Pakistan and the incidence has not declined over the years. It is responsible for 18.6% mortality due to maternal death. Hypertension in pregnancy occurs in 3 forms.

(1) Chronic hypertension: Persistently increased BP before 20th week of gestation.

(2) Pregnancy induced hypertension (PIH): Hypertension occurring after 20th week of gestation and up to 12 weeks post gestation.

- Pre-eclampsia: hypertension associated with proteinuria (= >300 mg/24 hours and edema)
- Eclampsia: severe pre-eclampsia with seizures (a life threatening situation)

(3) Gestational Hypertension: after second half of pregnancy without proteinuria. Usually settles 6 weeks post-delivery

Women should be evaluated in detail before a planned pregnancy, although it is a difficult proposition in all developing countries. Women in the child bearing age should not be given ACEI or ARB due to teratogenic potential.

Women also experience more hypertension when using oral contraceptives (OC). They need to be followed for BP check while on OCs. The Nurses' Health Study found that current users of oral contraceptives had a significantly increased risk of hypertension (relative risk [RR] 1.8; 95% confidence interval [CI] 1.5 to 2.3) compared with non-users.

Hypertensive disorders in pregnancy are a major cause of maternal, fetal and neonatal morbidity and mortality. It is critical to differentiate pre-eclampsia, a pregnancy-specific syndrome of exaggerated vascular constriction and reduced organ perfusion, from pre-existing chronic hypertension. Women with Stage 1 hypertension are at low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only, as there is no evidence that pharmacological treatment improves neonatal outcomes. Further, BP usually falls during the first half of pregnancy; therefore, hypertension may be easier to control with reduced or no medications. With lifestyle modifications, aerobic exercise should be restricted, on the basis of theoretical concerns that inadequate placental blood flow may increase the risk of pre-eclampsia, and weight reduction should not be attempted, even in obese pregnant women. Although the data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for those with primary hypertension. Use of alcohol and tobacco must be strongly discouraged. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs, in Stage 1 and 2, hypertension in pregnancy showed a direct linear relationship between treatment-induced fall in mean arterial pressure and the proportion of small-for-gestational-age infants. This relationship was independent of type of hypertension, type of antihypertensive agent and duration of therapy. With BP level less than 160/100 mm Hg without proteinuria, the patient can be observed and drugs can be withheld. However, for pregnant women with target organ damage or a prior requirement for multiple antihypertensive agents for BP control, antihypertensive medication should be continued as needed to control BP. In all cases, treatment should be reinstituted once BP reaches 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic, in order to prevent increases in BP to very high levels. Aggressive treatment of severe chronic hypertension in the first trimester is critical, since fetal loss rates of 50% and significant maternal mortality have been reported in these patients. Most of the poor outcomes are related to superimposed pre-eclampsia.

The primary goal of treating chronic hypertension in pregnancy is to reduce maternal risk, but the choice of antihypertensive agent(s) is largely driven by the safety of the fetus. Methylodopa is preferred by many as first-line therapy, based on reports of stable uteroplacental blood flow and fetal hemodynamics and the absence of long-term (7.5-year follow-up) adverse effects on development of children exposed to methylodopa in utero. Hydralazine, diltiazem, clonidine, prazosin, propranolol and labetalol are deemed safe. Diuretics should be used with caution in order not to cause placental hypoperfusion.
In the lactation phase, diuretics may decrease milk production through volume depletion. (Table 21)

### Table 21: Drug Treatment in Pregnancy

<table>
<thead>
<tr>
<th>First-line Agent</th>
<th>Methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line Agent</td>
<td>Nilendipine, Hydralazine, Diltiazem, Clonidine</td>
</tr>
<tr>
<td>(In case combination is needed with methyldopa)</td>
<td></td>
</tr>
<tr>
<td>Third-line Agent</td>
<td>Alpha &amp; Beta-blockers, Labetalol, Prazocine</td>
</tr>
<tr>
<td>Drugs to be avoided</td>
<td>Thiazide diuretics, ACEIs, ARBs</td>
</tr>
</tbody>
</table>

Prevention of pre-eclampsia relies on identification of high-risk women and close clinical and laboratory monitoring aimed at its early recognition, and institution of intensive monitoring or delivery when indicated. Treatment of pre-eclampsia includes hospitalization for bed rest, control of BP, seizure prophylaxis in the presence of signs of impending eclampsia, and timely delivery. Importantly, many women with pre-eclampsia have previously been normotensive, so acute BP elevations even to modest levels (i.e., 150/100 mm Hg) may cause significant symptomatology and require treatment. Treatment does not alter the underlying pathophysiology of the disease, but it may slow its progression and provide time for fetal maturation. Pre-eclampsia rarely remits spontaneously and in most cases worsens with time. In case of pre-eclampsia where delivery is more than 48 hours away then the above mentioned oral drugs will suffice. However, with urgent delivery, IV drugs are preferred. As all drugs are secreted in the milk, for mothers who want to feed, drugs may be withheld and patient BP followed closely.²⁹

### 5.3 Diabetes Mellitus:

The concordance of hypertension and diabetes is increased in the population; hypertension is disproportionately higher in diabetes.¹⁰¹ while persons with elevated BP are 2.5 times more likely to develop diabetes within 5 years.¹⁰² Epidemiological analyses show that blood pressures of 120/70 mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of 130/80 mmHg is reasonable if it can be safely achieved. There is no threshold value for blood pressure and risk continues to decrease with the normal range.¹⁰³ The same non-pharmacological interventions are recommended as for the hypertensive patients alluded to in the section above. For pharmacologic therapy, it is noted in trials that patients with hypertension (systolic blood pressure of 140 or diastolic blood pressure of 90 mmHg) should receive drug therapy in addition to lifestyle and behavioral therapy. Multiple drug therapy (two or more agents in proper doses) is generally required to achieve blood pressure targets. Patients with a systolic blood pressure of 130-139 mmHg or a diastolic blood pressure of 80-89 mmHg should be given lifestyle and behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, in addition, be treated with pharmacological agents that block the renin-angiotensin system. Initial drug therapy for all patients with a blood pressure of 140/90 mmHg or more should be with a drug class demonstrated to reduce CVD events in patients with diabetes ACE inhibitors and ARBs should be drugs of first choice. However, in cases of intolerance or lack of control of BP with those drugs, other classes of antihypertensives like beta-blockers and calcium channel blockers could be used.

### Table 22: Medication Choices in Diabetes

<table>
<thead>
<tr>
<th>BP in Diabetics</th>
<th>Antihypertensive to be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 140/90 mmHg</td>
<td>ACE-I or ARB in optimum dose</td>
</tr>
<tr>
<td>If response is inadequate</td>
<td>Add Thiazide Diuretic</td>
</tr>
<tr>
<td>If still no normalization</td>
<td>Add GCB and/or Beta blocker</td>
</tr>
</tbody>
</table>

If targets blood pressure still not achieved, a thiazide diuretic should be added. If, ACE inhibitors, ARBs, or diuretics are used, monitor renal function and serum potassium levels. In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In those with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency, ARBs have been shown to delay the progression...
of nephropathy. In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110–129/65–79 mmHg are suggested in the interest of long term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. Before beginning treatment, patients with elevated blood pressure should have their blood pressure re-examined within 1 month to confirm the presence of hypertension. Systolic blood pressure of 160 mmHg or diastolic blood pressure of 100 mmHg, however, mandates that immediate pharmacological therapy be initiated. Other risk factors should also be evaluated and controlled. 

8.4 Chronic Renal Failure

1. GFR below 60 ml/min / 1.73 m² (corresponding approximately to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women)
2. The presence of albuminuria (>300 mg/day or 200 mg albumin/g creatinine)

The goal of treatment is to slow deterioration of renal function and prevent CVD. Hypertension appears in the majority of these patients and is difficult to treat often requiring three or more drugs to reach target BP values of <130/80 mmHg. ACEIs and ARBs have demonstrated favorable effects on the progression of diabetic and nondiabetic renal disease. A limited rise in serum creatinine of as much as 35 percent above baseline with ACEIs or ARBs is acceptable and is not a reason to withhold treatment unless hyperkalemia develops. With advanced renal disease (estimated GFR <30 ml/min /1.73 m², corresponding to a serum creatinine of 2.5–3 mg/dL), thiazide diuretics need to be replaced with increasing doses of loop diuretics in combination with other drug classes.

8.5 Neurological Diseases

CVA / Stroke:

Effective therapy with antihypertensives reduces mortality due to stroke by 40%. All classes of antihypertensives have been shown to be effective in reducing stroke. Relative differences in the degree of stroke reduction are small.

Emergencies:

Neurologic emergencies due to very high level of blood pressure are the most difficult to distinguish from one another. Hypertensive encephalopathy is typically a diagnosis of exclusion since hemorrhagic and thrombotic strokes are usually diagnosed by demonstrating focal neurologic deficits and a corroborating computed axial tomographic or magnetic resonance imaging scan of the head. Subarachnoid hemorrhage is most easily diagnosed after lumbar puncture and or CT scan. Hypertension associated with head trauma (Cushing's reflex) usually has a typical history and corroborating physical findings to assist in the diagnosis, but the BP goal is controversial. The management of each of these conditions is somewhat different. Sodium nitroprusside is still the drug typically chosen for encephalopathy and can be used in other conditions, but nimodipine has both antihypertensive and anti-ischemic effects and improved long-term outcomes in subarachnoid hemorrhage but not in ischemic stroke. In patients with subarachnoid hemorrhage, oral nimodipine lowered BP in about 5% of the patients; about 1% discontinued the drug because of this. Intravenous nimodipine is no longer used because of its propensity to precipitously lower BP. The goal BP during treatment also depends on the presenting diagnosis. BP lowering is warranted and therapeutic in hypertensive encephalopathy (for which the goal is typically a 10–25% reduction in mean arterial pressure) but relatively contraindicated for acute stroke in evolution (when most neurologists will not give an antihypertensive drug). The use of sublingual nitroglycerin, rampant in Pakistan, for very high level of BP, has no scientific basis and in fact it may carry significant risk due to sudden drop in BP. The goal of therapy should be to gradually lower BP and avoid postural hypotension.
8.6 Obesity / Metabolic Syndrome:

Obesity and Metabolic Syndrome are integral parts of each other. Metabolic Syndrome is characterized by central obesity, hyperinsulinemia, glucose intolerance, low HDL-C level and pro-inflammatory atherosclerotic state. In the Western population obesity is defined as a BMI of > 30 kg/m². Adult Treatment Panel III guidelines for cholesterol management defines the metabolic syndrome as the presence of three of more of the following conditions: abdominal obesity (waist circumference >38 inches in men or >35 inches in women), glucose intolerance (fasting glucose >110 mg/dL), BP >130/85 mmHg, high triglycerides (>150 mg/dL), or low HDL (<40 mg/dL in men or <50 mg/dL in women). However, in the South Asians population a BMI of 27kg/m² is now considered as obesity. Abdominal obesity, characterized by the accumulation of visceral adipose tissue, is a major risk factor for the development of hypertension. Abdominal obesity is also the principal risk factor for insulin resistance and the development of type 2 diabetes. Hypertension in obese individuals is, therefore, commonly complicated by the concomitant presence of dyslipidemia, hyperinsulinemia, impaired glucose tolerance and other facets of the metabolic syndrome. Furthermore, abdominal obesity is associated with a number of functional and morphological abnormalities including sodium retention, increased cardiac output, renal hypertension, endothelial dysfunction, left ventricular hypertrophy, microalbuminuria and elevated markers of inflammation. Recent data shows increased expression of angiotensin II–forming enzymes in adipose tissue and increased activity of the renin-angiotensin system has recently been implicated in the development of insulin resistance and type 2 diabetes. Accordingly, antihypertensive agents that block the renin-angiotensin system might be a beneficial strategy for treatment of obesity-related hypertension. Both angiotensinconverting enzyme inhibitors and angiotensin type-1 receptor blockers have been associated with favorable metabolic properties and end-organ protection in addition to their antihypertensive effects. Data from ongoing large trials will provide an indication of the protective and preventive effects of these treatment strategies while offering insights into the mechanisms linking obesity, hypertension and other facets of the metabolic syndrome. The recommendations for obese patients to lose weight through diet and exercise and to control risk factors. ACEI/ARBs may be a prudent first choice but more often than not a combination with other classes of antihypertensives will be required.

ELDERLY

Treatment recommendations for older people with hypertension, including those who have isolated systolic hypertension, should follow the same principles outlined for the general care of hypertension. In many individuals, lower initial drug doses may be indicated to avoid side effects; however, standard doses and multiple drugs are needed in the majority of older people to reach appropriate BP targets. Patients should be assessed for postural hypotension if symptomatic or in case of a dose escalation. A decrease in standing SBP >10 mmHg, associated with dizziness or fainting, is more frequent in older patients with systolic hypertension, diabetes and those taking diuretics or venodilators. (63)

8.7 Coronary Artery Disease (CAD) and Congestive Heart Failure:

CAD is the most common form of target organ damage. In addition to risk factor control and lifestyle modifications in patients with hypertension and stable angina pectoris, the first drug of choice is usually a BB; alternatively, long-acting CCBs can be used. (6) In patients with acute coronary syndromes (unstable angina or myocardial infarction), hypertension should be treated initially with BBs and ACEIs with addition of other drugs as needed for BP control. In post myocardial infarction patients, ACEIs, BBs, and aldosterone antagonists (AA) have proven to be most beneficial. (122, 123, 124, 125)

In early CHF, where there are no symptoms but demonstrable ventricular dysfunction with echocardiogram, ACEIs and BBs are recommended. (126, 127) For those with symptomatic ventricular dysfunction or end-stage heart disease, ACEIs, BBs, ARBs and aldosterone blockers are recommended along with loop diuretics. (122, 125, 129, 130, 131, 132, 133, 134, 135)
toxic thiocyanate and cyanide. Other agents that are growing in popularity include fenoldopam mesylate, nicardipine and labetalol.

In pregnant women, magnesium and nifedipine are commonly used. Most authors suggest a reduction in mean arterial pressure of about 10% during the first hour and a further 10 to 15% during the next 2 to 4 hours. Hypoperfusion can result if the BP is lowered too suddenly or too far (e.g., to < 140/90 mm Hg). The systolic BP (SBP) target for aortic dissection is < 120 mm Hg in the first 20 minutes. For this condition, a beta-blocker (typically esmolol) is recommended to reduce shear stress on the aortic tear along with an intravenous antihypertensive like nitroprusside to reduce BP. Oral antihypertensive therapy can usually be instituted after 6 to 12 hours of parenteral therapy and the patient can be moved out of the intensive care unit and consideration can be given to screening for secondary causes of hypertension. Long-term follow-up to assure adequate control of hypertension is necessary to prevent further target-organ damage and a recurrence of another hypertensive emergency.

<table>
<thead>
<tr>
<th>Table 24: TREATMENT OPTIONS FOR HYPERTENSIVE EMERGENCIES/CRISES</th>
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<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Nitroprusside</td>
</tr>
<tr>
<td>Labetalol</td>
</tr>
<tr>
<td>Nitrites</td>
</tr>
<tr>
<td>Hydralazine</td>
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<tr>
<td>Diazoxide</td>
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</tbody>
</table>
Patients who present as medical emergencies with very elevated BP can have one of three possible diagnoses. It is very important to distinguish these from each other because their prognoses differ greatly if left untreated.

8.8 True Hypertensive emergency:

<table>
<thead>
<tr>
<th>Table 23: LIFESTYLE MODIFICATIONS TO REDUCE BLOOD PRESSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Encephalopathy</td>
</tr>
<tr>
<td>• LV heart failure</td>
</tr>
<tr>
<td>• MI</td>
</tr>
<tr>
<td>• Unstable angina</td>
</tr>
<tr>
<td>• Dissection of aorta</td>
</tr>
<tr>
<td>• Severe Hypertension with stroke or sub arachnoid hemorrhage</td>
</tr>
<tr>
<td>• Severe pre eclampsia/eclampsia</td>
</tr>
</tbody>
</table>

At the highest risk (if left untreated) is a person with highly elevated BP and signs or symptoms of acute, ongoing target-organ damage. Such a person should have the BP reduced within minutes (typically with an intravenously administered drug in an intensive care unit). At the lowest risk is a person with highly elevated BP and no target-organ damage, who presumably has simply untreated or ineffectively treated stage II hypertension. This situation is never an emergency and does not need acute treatment but instead a referral to a site for ongoing care for chronic hypertension.

8.9 Hypertensive urgency:

Between these two above situations are patients with very elevated BP and only chronic target-organ damage. The optimal management of such individuals is controversial, although some such situations could be considered if the treating physician feels that it would be unsafe to leave the patient without lowering the BP. Under these circumstances, BP lowering may be done at a more leisurely pace (typically within hours to days), usually with oral medications and close follow-up.

Unfortunately, most of what is known about the natural history of patients who present with these conditions derives from the days when effective chronic antihypertensive drug therapy was not available and the incidence of the problem was much greater than it is today. There is, therefore, essentially no information from randomized, comparative clinical trials about the relative merits of different therapies, and there is very little long-term follow-up data from patients with these diagnoses. The recommended process of care includes brief, focused, neurologic and cardiovascular examinations, direct ophthalmoscopy, an electrocardiogram, a urinalysis, and blood for renal function testing (e.g., serum creatinine). Comparison of the patient's current results with previous findings (if any) will allow an appropriate decision to be made regarding the chronicity of the observed abnormalities. The specific level of BP is not a necessary or a sufficient condition for the diagnosis of a hypertensive emergency. Young patients with previously normal BP can occasionally have acute target-organ damage caused by elevated BP if it exceeds 180/110 mm Hg (e.g., in the setting of acute glomerulonephritis). Many patients with chronic but poorly treated hypertension present with BP in excess of 220/130 mm Hg and yet have no acute target-organ damage and need not be immediately treated in hospital with antihypertensive drugs.

8.10 Hypertensive crises:

Hypertensive crises may present with hemorrhagic, obstetric, renal, cardiac or neurologic manifestations, but prompt recognition of the condition and institution of rapidly acting parenteral therapy to lower the BP (typically in an intensive care unit) is widely recommended. Sodium nitroprusside is the most inexpensive agent with the longest track record of successful use in hypertensive emergencies but is metabolized to
9. **WHITE COAT HYPERTENSION**

White coat hypertension (also referred to as 'office hypertension', 
141 or 'isolated clinical hypertension') 142 is a term used to denote individuals who have blood pressures that are higher than normal in the medical environment, but whose blood pressures are normal when they are going about their daily activities. Like many other working definitions in clinical medicine, white coat hypertension is an arbitrary definition intended to assist clinicians by improving cardiovascular risk stratification, a key step in the management of patients with essential hypertension. 25, 31 By identifying a stratum of subjects at low risk of future cardiovascular disease because of a normal average daytime blood pressure outside the medical setting. 143, 144 Thus far, this definition is clear, but unfortunately it lacks the precision needed to make it clinically useful. Event-based studies have shown that the risk of future cardiovascular disease events is less in patients with white coat hypertension than in those with higher ambulatory blood pressure levels, after controlling for concomitant risk factors 145, 146, 147

Average daytime level of blood pressure above 135/85 mmHg should be regarded as definitely hypertensive and levels below 130/80 mmHg as normotensive. It seems reasonable, therefore, to define white coat hypertension as being present if the conventional blood pressure is consistently equal to or greater than 140/90 mmHg, with average daytime ambulatory blood pressure below 135/85 mmHg. Available data strongly suggest that white coat hypertension, when defined by low levels of daytime blood pressure, either ambulatory or self-measured, identifies subjects at a lower risk from target organ involvement than subjects with sustained hypertension. These subjects require regular and accurate check-up visits. 148

Patients with elevated blood pressure during the clinic visit and normal blood pressure during usual activities might be further characterized by the following three features:
(a) Absence of organ damage induced by hypertension
(b) Absence of hypertension-related risk of future cardiovascular disease
(c) Absence of blood pressure reduction with antihypertensive treatment.

The patient should be followed regularly and lifestyle changes should be instituted and risk profile should be modified.

10. **MASKED HYPERTENSION**

This is defined as office BP which is in the normal range and is discovered to be high only on assessing ambulatory BP. The cause is not known. 146 The occurrence of masked hypertension and the reverse phenomenon of white-coat hypertension in at least 10% of children and adults introduces the potential for misdiagnosing 20% of subjects who present to doctors to have blood pressure measured. This estimate, which is conservative, must surely make ABPM an indispensable investigation for the diagnosis and management of hypertension in children, adolescents and adults. Bobrie et al., have shown recently that self-measurement of blood pressure may also detect masked hypertension, but it will be necessary to show that both techniques are identifying similar patients. 150

11. **RESISTANT HYPERTENSION**

Table 25 indicates the potential causes of resistant hypertension

<table>
<thead>
<tr>
<th>Table 25: CAUSES OF RESISTANT HYPERTENSION</th>
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<tbody>
<tr>
<td>- Poor compliance/forgatfulness</td>
</tr>
<tr>
<td>- Persistence with lifestyle including smoking and obesity</td>
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<tr>
<td>- Drugs to counter anti hypertensive therapy e.g. NSAIDS, Lignocaine, steroids.</td>
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<tr>
<td>- Obstructive sleep apnea</td>
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<td>- Irreversible organ damage</td>
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<tr>
<td>- Volume overload</td>
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<tr>
<td>- Not enough D/L therapy</td>
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<tr>
<td>- Progressive Renal Insufficiency</td>
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<tr>
<td>- High salt intake</td>
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<tr>
<td>- Hyperaldosteronism</td>
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</tbody>
</table>
12. METHODS TO IMPROVE PATIENT COMPLIANCE

Table 26 highlights some of the ways to improve patient compliance to continue antihypertensive medication.

**Table 26: HOW TO IMPROVE COMPLIANCE WITH TABLETS**
- Educate patients about complication of hypertension and benefits of treatment and thus value of adherence
- If possible minimize the number of pills daily e.g. fix dose drugs
- Involve family in treatment plan
- Make use of self measurement of BP at home
- Explain the nature of side effects of drug and possible solutions

13. CONCLUSIONS

In summary, it would suffice to say that at the moment, hypertension has emerged as the most important cardiovascular risk factor with immense economic burden. It is a silent disease, therefore, it is often undiagnosed and presents with complications of cardiovascular nature. In Pakistan, we do not have a public level screening mechanism, which could pick out the silent cases. Over the years, with the meager local data we have, we know that we have under-diagnosed and under-treated this condition. We needed a well referenced document to help the policy makers as well as the clinicians to develop a broad based approach that could serve our people in a cost effective manner. We have presented the evidence in the above review but at junctures, we will have to depart from the main to treat in a system where the principal mode of finance is out of pocket payment. Therefore, economically priced and cost-effective drug therapy should be encouraged and availability of drugs like the thiazide diuretics should be ensured at the Drugs Controller level in the Ministry of Health. It is also imperative that we maintain a hypertension registry where, for example, drug side effects may be reported and in this way we will have local data that is lacking at this point in time. It is also felt that the essential drug list should be prepared and announced, and all evidenced based antihypertensive therapies should form a part of it. This will help maintain an evidence based drug list for procurement by the public health sector. We have stated this earlier and reiterate that our undergraduate syllabus needs to be revamped regarding management of hypertension. We also recommend registration of GPs in the country for regular CME activity in the CME register. For non-communicable diseases and risk factors it should be mandatory for the community and institution based physicians to achieve credit hours to maintain credentials. This is being done in other developing countries and we need to follow the example. Unless we train our first line of defense we will always be vulnerable.

We hope that this document that has been produced through consensus, its draft being presented in front of the committee on multiple occasions and the suggestions incorporated, will meet expectations and that it will become a nationally administered document. This will help us standardize care and make our care uniform across the country and make self audit at a later stage possible.


33. Park JB, Schiffrin EL. Small artery remodeling is the most prevalent (early?) form of target organ damage in mild essential hypertension. J Hypertens 2001; 19: 821-830.


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76. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358:1033-41.


