

# **3<sup>rd</sup> National Hypertension Guideline**

for the Prevention, Detection, Evaluation &  
Management of Hypertension



**Pakistan Hypertension League  
2018**



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**In the Name of Allah  
the most Gracious the Dispenser of Grace**

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### Writing committee PHL 2018 guideline:

- Dr. Aamir Hameed Khan (Chair)
  - Dr. Aysha Almas (Co-chair)
  - Dr. Hunaina Shahab (Secretary)
  - Dr. Abdul Ghaffar Khan (Member, Baluchistan)
  - Dr. Amber Ashraf (Member, KPK)
  - Dr. Asad Saleem (Member, Islamabad)
  - Prof. Feroze Memon (Member, Sindh)
  - Dr. Irfan Ellahi Chandna (Member, Sindh)
  - Prof. Saulat Siddique (Member, Punjab)
- 

## Advisory Board (National)

- Prof. Azahr M Farooqi
- Pro. Mohammad Ishaq
- Prof. A. Hafiz Chaudhri
- Prof. Ejaz A Vohra
- Prof. Nazir A Memon
- Prof. Khawar Kazmi
- Prof. M. Zaman Shaikh
- Prof. Feroz Memon
- Prof. Samad Shera
- Prof. Shehryar A Sheikh
- Prof. Wahid A. Sahibzada
- Prof. Abdus Samad
- Prof. Khalida Soomro
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- Prof. Abdul Basit
- Prof. Akbar Chaudhri
- Prof. M. Naeem Asalm
- Dr. Bashir Hanif
- Prof. Waris Qidwai
- Prof. Kalimuddin Aziz
- Dr. Shaukat M. Malik

## Advisory Board (International)

- Prof. Tazeen H. Jafar



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## Preface

Hypertension, best known as silent killer is the most common chronic illness worldwide affecting over 20% of the adult population. Over the past five decade the burden of non-communicable disease like hypertension and diabetes leading to the cardiac complication has gradually shifted from the developed world to under developed world. South Asia with its dense population and poverty is the hardest hit region of the world in this regard.

Once consider a condition hypertension is now regarded as the main contributor to heart attached and strokes making it the leading cause of death.

Pakistan medical research council, national health survey released the first authentic data on hypertension in 1997. This was an eye opener as 18% of population over the age of 15 years was found to be hypertensive in Pakistan.

Hypertension detection, management and treatment have been a gigantic challenge to the medical profession globally. To meet this challenge, the Pakistan Hypertension League was found in 1997.

Pharmacotherapy of hypertension has shown significant evolution in the past three decades

Today there are several antihypertensive classes of agents available in the market. What is the right drug for a patient in general, and what is the right drug for a particular patient? How to initiate and achieve blood pressure control?

These are major question faced by physicians today.

To address these matters international societies concerned with hypertension developed guidelines for the benefits of Physician based on large scale clinical trial in terms of safety, efficacy and cardiovascular protection.

PHL soon after its establishment invited experts in the field of medicine and prepared the first guideline in 1998. More than 100 senior members of medical fraternity representing all specialties of medicine took part in its preparation.

The second guideline was developed in 2009 under the chairmanship of Dr. Maqbool H. Jafri one of the founding father and most active member of PHL. I take this opportunity to pay rich tributes to late Dr. Maqbool H. Jafri for his academic contribution in the field of hypertension.

The field of hypertension is a dynamic subject with new evidences and question emerging and therefore, the guideline is always under constant review.

It is a great occasion that we are able to revise our guideline and come up with PHL III, 2018 guideline. Dr. Aamir Hameed Khan and his working group under the guidance of National Advisory Board have developed an excellent document taking into account all the latest data and international recommendations aimed at rational approach for optimal control of blood pressure as well as offering cardiovascular protection.

The guideline is there to help the primary physicians to treat the patient most efficiently and providing a quick reference to support the use of a particular agent.

It is hoped that this guideline will provide a firm scientific basis in the detection, treatment and control of hypertension in Pakistan.

Prof. Mohammad Ishaq  
MRCP, FRCP, FRCP (E), FACC, FCPS,  
Secretary General, Pakistan Hypertension League,  
Former President, Pakistan Hypertension League.



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## Message from the chairman of the writing committee:

Hypertension is arguably one of the most concerning problems of the 21st century, locally, regionally and globally. It is also one of the coronary artery disease risk factors that have the most evidence to date. Therefore, how we deal with this problem is vital, as there is enough in the form of good research data to guide our way forward. Why is it important to have guidelines for any condition? The quest is to have reasonable objectives and the means to achieve them. Guidelines help compliance to therapy and streamline and simplify processes to achieve the objectives in a cost effective and evidence based manner. The Pakistan Hypertension League (PHL) 2009 guideline was an effort to do the same. In 2018 we have newer evidence to suggest the fourth, fifth, sixth and even seventh line therapies. So it was thought that this year we would bring out an update on the PHL 2009 guideline. In these guideline we have made an effort to bring more national data that is relevant to our context and also to simplify steps and algorithms. It has been seen globally that when guidelines are made simpler they improve compliance. We have added a section with case vignettes in the form of a workshop and this has been done to make these guidelines into a working document that will be used clinically.

I would like to thank Professor Mohammad Ishaq, secretary general of the Pakistan Hypertension League for the confidence he has reposed in me for taking this great responsibility of chairing the writing committee and bring forward this 3rd draft of the guidelines. He has been a great mentor guide over the years in this journey from the 2nd to this current draft. I would also like to thank all members of the writing committee, who have contributed and enriched us with their invaluable suggestions and thoughts. I hope this document will be a useful document that will be used clinically and will not see dust on an archive shelf.

I wish the readers the very best for the future.

### Aamir Hameed Khan

MBBS, BSc, FCPS (med), FCPS (card), FACC  
Associate Professor of Medicine and Consultant Cardiologist  
Department of Medicine  
Aga Khan University  
Stadium Road, Karachi, Pakistan  
Tel: 92-21-34864700 Fax: 92-21-34932095  
Email: aamir.hameed@aku.edu



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## Table of Contents

1.0	Introduction	01
1.1.	Global Perspective	01
1.2.	Pakistani Perspective	01
2.0	Blood Pressure	04
2.1.	High Blood Pressure or Hypertension	05
2.2.	Signs and Symptoms of BP	05
3.0	Risk factors of hypertension	05
3.1.	Age	05
3.2.	Race/Ethnicity	05
3.3.	Overweight	05
3.4.	Gender	05
3.5.	Lifestyle Habits	06
3.6.	Family History	06
4.0	Measurement of blood pressure	06
4.1.	Mercury Sphygmomanometer	07
4.2.	Aneroid Apparatuses	07
4.3.	Automated Digital Sphygmomanometer	08
4.4.	The preferred device for the measurement of BP	09
5.0	Accurate method to measure BP	09
5.1.	Cuff Inflation Hypertension	10
6.0	Type of blood pressure and their significance	11
6.1.	Physicians' and Nurses' BP measurement	11
6.2.	Single versus multiple clinic readings and accuracy of BP	11
6.3.	In-clinic versus post clinic BP	11
6.4.	Home BP monitoring (HBPM)	12
6.5.	Ambulatory BP monitoring	12
7.0	Risk of elevated BP	13
7.1.	Treatment threshold and target values	13
8.0	Diagnosis of hypertension	17
9.0	Diagnostic Work-Up	19
9.1.	Target organ damage	19
10.0	Why treat blood pressure?	20
11.0	Hypertension	21
11.1.	Threshold for diagnosis and treatment:	22
12.0	Global risk assessment	25
12.1.	Risk calculator	26
12.2.	Recommendations	26
12.3.	Implications of risk calculation	26
13.0	Role of ASA for the primary prevention of CV disease	27
14.0	Role of statin therapy	28
15.0	Life style modifications	28
15.1.	Body Mass Index and Waist Circumference	28
15.2.	Exercise	30
15.3.	Complementary and Alternative Medicine	31
15.4.	Weight loss	31
15.5.	Salt intake	32
15.6.	Smoking cessation and other tobacco use	32
15.7.	Nutrients, vitamins and fish oil	32



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16.0	Drugs to treat hypertension	34
16.1.	Algorithmic approach to the treatment of hypertension	35
16.2.	Combination therapy: (New Onset Diabetes)	36
16.3.	Combination therapy: (free versus fixed dose combination)	36
16.4.	Resistant Hypertension	36
17.0	White Coat Hypertension (WCH), White Coat Effect (WCE) or White Coat Syndrome (WCS)	39
17.1.	Masked Hypertension (MH)	40
18.0	Hypertension crises	41
18.1.	Severe hypertension without TOD	41
18.2.	Hypertensive urgency	42
18.3.	Hypertensive Emergency	42
19.0	Pregnancy and hypertension	44
19.1.	Diagnosis of HTN in pregnancy	45
19.2.	Treatment of HTN in pregnancy	46
19.3.	Antihypertensive Drugs to Treat Severe Hypertension in Pregnancy	48
20.0	Hypertension in the elderly	49
20.1.	Isolated systolic hypertension	49
20.2.	Effect of age on BP	50
20.3.	Drug Therapy	50
20.4.	Problem of orthostatic hypotension	50
20.5.	Problem of frailty	51
20.6.	Goal BP	52
21.0	Hypertension in the pediatric population	53
21.1.	Measurement	53
21.2.	Diagnosis	53
21.3.	Cuff size	54
21.4.	Management of hypertension in the pediatric population	54
22.0	Secondary Hypertension	56
23.0	Follow-up	57
24.0	Special concerns	57
24.1.	Use of sublingual drugs to lower BP acutely	57
24.2.	Use of anxiolytics as first line antihypertensive therapy	57
25.0	Summary/Conclusion	58
26.0	Case Vignettes	60
27.0	Pakistan Hypertension League Glimpses	65





## 1.0 Introduction:

Hypertension is one of the most preventable causes of premature morbidity and mortality worldwide [1]. Untreated hypertension is associated with a progressive rise in BP, resulting in a treatment resistant state due to associated vascular and renal damage [1].

### 1.1 Global Perspective

Around 31% of the global population i.e. 1.4 billion people worldwide are diagnosed to have hypertension; its prevalence being significantly lower in the higher income countries (28.5%) compared to the lower and middle income countries (31.5%) [2]. It is predicted that the number of people diagnosed with hypertension will increase to about 1.6 billion by the year 2025 [3]. Therefore hypertension poses a significant challenge to the public health sectors worldwide, with the bulk of the burden lying in the lower to middle income countries where the prevalence of this silent killer is increasing while decreasing in the higher income countries [2]. Blood pressure levels have particularly increased over the years in South and Southeast Asia, East and West Africa and Oceania regions [2-4]. Suboptimal blood pressure costs about 10% of the world's total healthcare budgets and if the current scenario remains, uncontrolled blood pressure can cost about 1 trillion dollars worldwide in health expenditures [5]. Adequate control of hypertension is an important avenue for public health sector globally.

### 1.2 Pakistani Perspective

The National Health Survey of Pakistan from 1990 to 1994 reported that 19% of people in the country have hypertension, with every third person over the age of 45 years being hypertensive [6]. More recent data suggest that the overall prevalence of hypertension has increased to 34% [7]. Awareness rate of this chronic disease has steadily increased from 15% in men and 36% in women [6] in 1990 to 1994 to 42% in 2002 [8] and to 62% in 2017 [7]. Of more concern is that half the people with hypertension are diagnosed and that 50% of the ones diagnosed are actually treated for it [9, 10]. Amongst children between the ages of 5 to 17 years, the prevalence of hypertension is 3.4% [6]. As the age of the people increases, the prevalence of hypertension also escalates, rising steeply after 20 to 29 years of age to more than 60% after the age of 70 years [6,11]. Amongst both genders, more women suffer from hypertension in Pakistan [7]. Amongst the different ethnicities settled in Pakistan, Baluchi's are found to have the highest prevalence of hypertension (25% in men and 41% in women) followed by Pashtuns (24% in men and 25% in women). Sindhis (19% in men and 9% in women) and Punjabis (17% in men and 16% in women) were found to have the least prevalence of hypertension [12], although still high. In one study, urban dwellers were found to have more hypertension compared to rural dwellers but after adjusting the results for body mass and waist circumference, there was no difference [12]. The factors that strongly correlate with hypertension in Pakistani population includes increasing age, female gender, comorbid conditions like diabetes mellitus, chronic kidney disease, cardiovascular diseases, body mass index and family history of hypertension [7], The age and BMI displayed a quantitative association [13].



**Control of Blood Pressure and Risk Attenuation (COBRA) and Control of Blood Pressure and Risk Attenuation- Bangladesh, Pakistan and Sri Lanka (COBRA- BPS) Trials in the evolving knowledge base of Hypertension management in the country.**

The increasing prevalence of hypertension creates a significant health problem for Pakistan. Economically efficient methods are required to control this growing problem in an already resource scarce country. The largest hypertension study took place between 2004 and 2007, a cluster randomized controlled trial [14] the Control of Blood Pressure and Risk Attenuation (COBRA) trial was conducted amongst 1341 patients, aged more than 40 years, with systolic blood pressure  $\geq 140$ mmHg and diastolic blood pressure  $\geq 90$ mmHg from 12 randomly selected communities from the low to middle income areas of urban population of Karachi. These patients were randomized to four different groups of two community based interventions, i.e. home health education (HHE) from lay health workers every 3 months and training of general practitioners (GP) in the management of hypertension every year. The patients were assigned to any one of the groups (HHE plus GP, HHE alone, GP alone versus no intervention/usual care). At the end of a 2-year follow-up, there was a significant reduction of 10.8 mmHg in systolic BP levels in the HHE plus GP group over either of the two interventions alone or no intervention/usual care group [14]. It was also found that the combination of HHE plus trained GP was most cost efficient in the management of hypertension (cost analysis), specifically with an incremental cost-effectiveness ratio of \$23 per mm Hg reduction in systolic BP compared with usual care. This suggested that community based interventions can be utilized at government level in the management of hypertension in South Asian countries [15].

In order to demonstrate a sustained effect of reduction in BP, a 7-year follow-up [16] was conducted on the 1341 patients recruited in the COBRA trial. It was found that although the reduction in BP effect had attenuated but was still statistically significant at the 7-year follow-up. Those patients who received the HHE plus trained GP intervention were found to have 2.1mmHg lower than the no intervention/usual care group. Interestingly, the HHE plus GP intervention group had a greater decrease in LDL levels over the usual care/no intervention group. In resource poor countries, this cost effective strategy may be employed by the policy makers to control this burgeoning burden of hypertension with its dreaded complications. This could be done utilizing the current health care infrastructure without significantly altering the system logistics [16].

The COBRA trial was conducted in the urban area of Pakistan, however majority of the South Asian countries comprise of rural areas (Pakistan 64%, India 71%, Bangladesh 73% and 85% Sri Lanka) [17]. Therefore, in order to test this in the rural population the investigators extended the scope to the rural areas and made this initiative a regional one. This led to the COBRA – BPS (Control of Blood Pressure and Risk Attenuation – Bangladesh, Pakistan and Sri Lanka) feasibility study, which was conducted to assess if this evidence based approach could be adapted for use in the existing primary health care infrastructure in three South Asian countries - Bangladesh, Pakistan and Sri Lanka [17]. It was aimed to pilot test the multicomponent intervention (MCI) in rural areas of Bangladesh, Pakistan and Sri Lanka. The MCI composed of BP screening by trained community health workers and checklist guided referral to a trained provider,



home health education by trained government health workers and documentation via a checklist, algorithm based training of private and public hypertension management providers. The feasibility study was conducted on 412 participants aged more than 40 years with systolic BP  $\geq 140$ mmHg and diastolic BP  $\geq 90$ mmHg amongst 9 rural areas of Bangladesh, Pakistan and Sri Lanka. At three months' post-intervention, the results demonstrated a 4.5mmHg drop in the systolic blood pressure in the overall pooled analysis in the three countries with a 10.5mmHg drop in systolic BP amongst those who had uncontrolled BP. The MCI model is feasible for operation in the rural areas of the low-income South Asian countries using the already established primary healthcare system. This is strongly adhered to by patients and is accepted by stakeholders [17]. The full scale cluster randomized controlled COBRA-BPS trial is proceeding currently amongst 30 clusters (10 each in Bangladesh, Pakistan and Sri Lanka) to evaluate the effectiveness and cost-effectiveness of the MCI model for decreasing BP in rural areas of the three South-Asian countries [18]. A sub-study of the COBRA trial follow-up, where echocardiograms and lab parameters were performed at 7 years revealed higher baseline albuminuria, lower baseline eGFR, and their longitudinal worsening over 7 years, which were significantly associated with higher left ventricular mass index (LVMI) or the development of LVH among individuals with hypertension [19]. Already this landmark effort has taught us that for BP control a home health education and physician training can help attain sustained BP lowering effect as shown by decreased BP values and other hard parameters like albuminuria and LVH.

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## 2.0 Blood pressure (BP):

When heart beats, it pumps blood round the body to give it the energy and oxygen it needs. As the blood moves, it pushes against the sides of the blood vessels. The strength or lateral pressure applied to the vessel wall is called blood pressure (BP). If BP is too high, it puts extra strain on the arteries and this may lead to complications. BP has two readings the upper one is the systolic BP and the lower one is the diastolic reading [2].



## 2.1 High Blood Pressure or Hypertension:

Hypertension is when the blood pressure readings are consistently 140 over 90, or higher, over a number of weeks taken according to a planned protocol of clinic visits. Hypertension may also be present if just one of the numbers is higher than the threshold limit of either 140 or 90 mmHg taken according to a planned protocol of scheduled clinic visits. Consistently raised BP can cause complications that include but are not limited to the brain, heart, eyes, kidneys and the vasculature [3].

## 2.2 Signs and Symptoms of BP:

There are no usual signs and symptoms of BP and therefore it is called the “silent killer”. However signs and symptoms are noted when the side effects or complications associated with high BP occur like chest pain due to myocardial infarction, “thunderclap” headache associated with brain hemorrhage, paralysis or weakness of a part of the body in case of a stroke etc. [4].

## 3.0 Risk factors for hypertension:

Anyone can develop high BP; however, age, race or ethnicity, being overweight, gender, lifestyle habits, and a family history of high blood pressure can increase the risk for developing high blood pressure.

### 3.1 Age:

Blood pressure tends to rise with age. About 65 percent of people, who are age 60 or older are seen to have high BP. However, the risk is continuously changing with rise in the number of overweight children and teens thus seeing the onset of hypertension at an earlier age [5].

### 3.2 Race/Ethnicity:

High BP is more common in African American adults than in Caucasian or Hispanic American adults. [6] South Asians of which Pakistan makes a part behave more like their Caucasian counterparts compared to the Afro-Caribbean subgroup in the United Kingdom (UK). However, the prevalence of hypertension in the South Asian population is the same as in the white population in the UK, with the Pakistani group being intermediate to that of the Indians (higher) and the Bangladeshis (lower) [7].

**3.3 Overweight:** Overweight and obese individuals are more prone to developing hypertension. The terms “overweight” and “obese” refer to body weight that’s greater than what is considered healthy for the height [8].

**3.4 Gender:** Before age 55, men are more likely than women to develop high blood pressure. After age 55, women are more likely than men to develop high blood pressure [8].



### 3.5 Lifestyle Habits: [8]

Unhealthy lifestyle habits can raise BP, and they include:

- Excess (salt) sodium or too little potassium
- Lack of physical activity
- Smoking
- Drinking too much alcohol
- Stress

**3.6 Family History:** A family history of hypertension raises the risk of developing hypertension. Some individuals have a high sensitivity to sodium and salt, which may increase their risk and may run in families. Genetic causes from the basis why family history is a risk factor for this condition [8].

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### 4.0 Measurement of blood pressure (apparatuses):

Blood pressure can be measured using many different types of BP apparatuses like the mercury, aneroid and digital apparatuses. The devices need to be validated by the American Association of Medical Instrumentation (AAMI), British Hypertension Society (BHS) or the European Society of Hypertension (ESH). The devices also need to be calibrated to ensure accuracy of the measurement [1].





#### 4.1 Mercury Sphygmomanometer: [2]

BP readings produced by a conventional sphygmomanometers based on mercury is considered as the golden standard. These devices are extensively validated. Mercury based apparatuses have been banned in many countries due to the toxicity associated with the metal. However, some exceptions have been made for medical devices like conventional sphygmomanometers for the time being but in due course of time these will be phased out. The measuring unit has a transparent tube containing mercury that is calibrated and marked in millimeters of mercury (mmHg). These devices are very delicate and special care should be taken while operating, storing or transporting the unit. Accidental dropping of the unit can result in the rupture of the mercury containing tube and the spilling of the toxic mercury metal.

##### 4.1.1 Advantages of Mercury Sphygmomanometers

- It is simple and durable. If properly used, this device can be used for a lifetime.
- This device can produce accurate readings and does not require any readjustments or regular recalibrations.

##### 4.1.2 Disadvantages of Mercury Sphygmomanometers

- It is a bulky medical device prone to damage to the mercury containing tube.
- Operating this requires practice and is not suitable for household use.
- People with hearing or visual disabilities cannot use this device.

#### 4.2 Aneroid Apparatuses: [2,4]

Aneroid means “without fluid”. These devices do not use mercury and are considered as a safer alternative when compared to mercury based devices. However these devices are not widely validated. The recording procedure is very similar to a conventional mercury based device requiring inflating and deflating the cuff. The device consists of cuff that is attached by tubes to a dial gauge marked in millimeters of mercury (mmHg). Inside the gauge head the device uses mechanical parts to convert the cuff pressure into a gauge based reading. There are few devices that have been validated in studies, while most devices tested were not noted to be accurate [5].

##### 4.2.1 Advantages of Aneroid Sphygmomanometers

- They are cheaper, more portable and less expensive compared to mercury sphygmomanometers
- The aneroid gauge can be placed in any position for easy reading.
- The may also come with built in stethoscope.
- The aneroid gauge can be attached to the cuff for single hand operation of the device.

##### 4.2.2 Disadvantages of Aneroid Sphygmomanometers

- The aneroid gauge is a delicate mechanism. Special care should be taken to prevent accidental bumping or dropping of the gauge.
- Aneroid gauges require periodic cross checking with mercury sphygmomanometer to make sure that the internal mechanisms are working perfectly. It may require recalibration if the device is giving faulty reading.



- People with hearing or visual disabilities cannot use the device.
- Operating aneroid sphygmomanometers requires practice.

### 4.3 Automated Digital Sphygmomanometer: [6]

Oscillometric devices are commonly referred as automatic digital sphygmomanometers. These devices use an electronic pressure sensor for measuring the BP and the readings are given out digitally on a display.

These devices have inflatable cuffs like Mercury or Aneroid devices and the cuff is attached to the electronic unit. However, the main difference is in the technique used for measuring the blood pressure. Whereas, the mercury or aneroid device reports are based on the sounds produced by the blood flowing inside the arteries. Digital devices evaluate and measure the oscillations of the arteries using pressure sensors. These devices are widely validated.

As the cuff is inflated and then deflated later, oscillations occurs. These oscillations are processed using an algorithm to produce systolic and diastolic values that are digitally displayed on the device display. Automatic digital devices are usually battery operated.

**4.3.1 Wrist blood pressure monitors:** These are digital blood pressure monitors that work similar to upper arm BP monitors but the results are not widely validated [6]. It can be used by individual, who find arm based devices uncomfortable or painful. However, these are not recommend for everyone, due to the possibility of receiving false reading due to improper use. BP monitors are very sensitive to body position and special care should be taken during their use in order to get accurate readings.

### 4.3.2 Advantages of automatic digital sphygmomanometers

- The device is very compact and portable.
- Operating the device is extremely easy and this is the preferred device of choice for personal monitoring at home.
- Since most of the critical operations are done automatically during the recording process, chances of human error are minimum.
- Removes the threat of the “alert response” as it does not need medical staff to be present.
- It can save serial readings.

### 4.3.3 Disadvantages of Automatic Digital Sphygmomanometers

- The device is delicate and proper care should be taken while handling the device.
- Repairing the device can be complicated and in most cases the device has to be serviced by the manufacturer.
- Even the most advanced devices can produce incorrect reading with some individual.
- It necessary to periodically counter check with conventional Mercury sphygmomanometers for accuracy.





**4.4 The preferred device for the measurement of BP:** It is now recommended to use the oscillometric digital automated BP apparatus. This allows for serial readings and does not need the staff to be there and this minimizes the alert response.

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## 5.0 Accurate method to measure BP: Adapted from the American Heart Association guidelines of the management of hypertension. [1]

### Step 1 - Choose the right equipment:

The following will be needed:

1. Quality stethoscope
2. An appropriately sized BP cuff [table 1]
3. Validated and calibrated BP apparatus

Table 1. Selection Criteria for BP Cuff Size Measurement of BP in Adults

Arm Circumference	Usual cuff size
22 - 26 cm	Small adult
27 -34 cm	Adult
35 - 44 cm	Large adult
45 - 52 cm	Adult thigh

Adapted from Pickering TG, et al. *Circulation* 2005;111:607-716.



**Step 2** - Prepare the patient: Prepare the patient: Make sure the patient is relaxed by allowing 5 minutes to relax before the first reading. The patient should sit upright with their upper arm positioned so it is level with their heart and feet flat on the floor. Remove excess clothing that might interfere with the BP cuff or constrict blood flow in the arm. Be sure you and the patient refrain from talking during the reading.

**Step 3** - Choose the proper BP cuff size: Choose the proper BP cuff size: Most measurement errors occur by not taking the time to choose the proper cuff size. Wrap the cuff around the patient's arm and use the INDEX line to determine if the patient's arm circumference falls within the RANGE area. Otherwise, choose the appropriate smaller or larger cuff.

**Step 4** - Place the BP cuff on the patient's arm: Palpate/locate the brachial artery and position the BP cuff so that the artery marker points to the brachial artery. Wrap the BP cuff snugly around the arm.

**Step 5** - Position the stethoscope: On the same arm that you placed the BP cuff, palpate the arm at the antecubital fossa (crease of the arm) to locate the strongest pulse sounds and place the bell of the stethoscope over the brachial artery at this location.

**Step 6** - Inflate the BP cuff: Begin pumping the cuff bulb as you listen to the pulse sounds. When the BP cuff has inflated enough to stop blood flow you should hear no sounds through the stethoscope. The gauge should read 30 to 40 mmHg above the person's normal BP reading. If this value is unknown you can inflate the cuff to 160 - 180 mmHg. (If pulse sounds are heard right away, inflate to a higher pressure.)

**Step 7** - Slowly Deflate the BP cuff: Begin deflation. It is recommended that the pressure should fall at 2 - 3 mmHg per second, anything faster may likely result in an inaccurate measurement.

**Step 8** - Listen for the Systolic Reading: The first occurrence of rhythmic sounds heard as blood begins to flow through the artery is the patient's systolic pressure. This may resemble a tapping noise at first.

**Step 9** - Listen for the Diastolic Reading: Continue to listen as the BP cuff pressure drops and the sounds fade. Note the gauge reading when the rhythmic sounds stop. This will be the diastolic reading. If the sound continues to zero as may be in the case of stiff arteries, then the point where the sounds become muffled is taken as the diastolic limit.

**Step 10** - Double Check for Accuracy: It is recommended taking a reading with both arms and averaging the readings. To check the pressure again for accuracy wait about five minutes between readings. Typically, blood pressure is higher in the mornings and lower in the evenings.

**5.1 Cuff Inflation Hypertension:** The muscular activity used to inflate the cuff can acutely raise the BP by as much as 12/9 mmHg, an effect called cuff inflation hypertension that dissipates within 5 to 20 seconds (average 7 seconds in one study) [2]. A single clinic or home systolic BP of 120 to 157 mmHg had less than an 80 percent chance of correctly classifying the patient as being in or out of control [3].



## 6.0 Types of BP and their significance:

There are multiple types of BP measurements like office or clinic BP, ambulatory BP, nocturnal BP etc. Most research has relied on in-clinic or office BP. However, these readings are the least predictive of adverse outcomes. It is noted that ambulatory measurement of BP is superior to clinic measurement in predicting cardiovascular mortality, and nighttime (nocturnal) BP is the most potent predictor of outcome [4]. Interestingly, in the ASCOT BPLA it was noted that the Amlodipine based arm was better than the Atenolol based arm despite statistically non-significant difference in the mean brachial BP in both the arms. BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP. Moreover, central aortic pulse pressure may be a determinant of clinical outcomes, and differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the 2 BP treatment arms in ASCOT BPLA [5]. Furthermore, in the ASCOT BPLA both clinic BP and ABP were significantly associated with rates of cardiovascular events. ABP nocturnal pressures provided complimentary and incremental utility over clinic BP in the prediction of cardiovascular risk in treated hypertensive patients. These data support the use of ABP to assess the effect of antihypertensive treatment in clinical practice [6].

### 6.1 Physicians' and Nurses' BP measurement:

It is noted that the readings taken by physicians and nurses in the clinic are different. The readings taken by the physicians were higher than that of the nurses. This is a display of the alert response noted in the clinic setting. Large between-physician differences exist in the magnitude of the white-coat effect that cannot be explained by patient characteristics. Physicians should therefore not make any decisions based on BP measured manually during a first encounter [7].

### 6.2 Single versus multiple clinic readings and accuracy of BP:

It has been shown that the error of overestimation of BP inherent in cuff blood pressure measurement by a physician cannot be avoided by repeated visits by the physician over a short time span. It clearly can be reduced, however, if a nurse performs BP measurements [8].

### 6.3 In-clinic versus post clinic BP:

In a study where in-clinic BP was compared to BP measurement taken 15 minutes after a clinic encounter (post clinic BP), Shahab et al showed that BP readings taken in the post-clinic setting may significantly be the lowest reading in a clinic encounter, making in-clinic BP unreliable to diagnose or manage hypertension [9]. Furthermore, Shahab et al, correlated in another study [10] the post-clinic BP with daytime ABP mean readings. They demonstrated that in-clinic BP is falsely elevated and post-clinic BP is the lowest reading in a real-world patient-physician encounter and it is an important surrogate of ABPM. Therefore, they suggest that post-clinic BP be employed for diagnosis and management of hypertension. This suggestion is also viable in a health care set-up where ABP is not freely available and accessible to the population.



#### 6.4 Home BP monitoring (HBPM):

The PHL follows the widely practiced recommendation for home monitoring by the National Institute for Clinical Excellence (NICE) guideline [11]. It is recommended that when using HBPM to confirm a diagnosis of hypertension it is necessary to ensure that:

- For each BP recording, two consecutive measurements are taken, at least 1 minute apart with the person seated
- BP is recorded twice daily, ideally in the morning and evening (pre-breakfast and pre-dinner)
- BP recording continues for at least 4 days, ideally for 7 days.

Measurements taken on the first day should be discarded and the average value of the remaining days after day one values are discarded should be used. Except for special cases (for example, patients with arrhythmias, the use of auscultatory devices (mercury, aneroid or other) is not recommended for HBPM. [12] Monitors that use the oscillometric method are accurate, reliable and easy to use. The British Hypertension Society has produced list of validated devices. [13] It recommended that semiautomated (manual cuff inflation) or automated electronic devices that measure BP at the upper arm are preferred for HBPM. Such devices are easier to use and avoid observer bias. Monitors equipped with an automated memory should prevent patients from misreporting their BP measurements. Finger and wrist devices are less accurate and are not recommended, unless brachial measurements are difficult or impossible to obtain (for example, in subjects with very large arm circumference or extreme obesity).

#### 6.5 Ambulatory BP monitoring: [11]

This method of BP measurement is the gold standard. It takes multiple readings; the studies deem any where from 70% to 85% successful readings to render the study interpretable. Different BP readings can be acquired. The over all mean reading is the average of all readings and the normal range is <130/80 mmHg. The nocturnal BP is very important, as it is significantly associated with target organ damage. The nighttime normal value is <120/70 mmHg. The nighttime periods show the dipping pattern that is normally at least 10% drop in BP at nighttime as compared to daytime BP (comparing means). The nighttime period also shows the morning surge, a period of vulnerability as strokes and MIs happen quite often at . or around this time. The daytime mean normal BP is <135/85 mmHg. This tool is vital in the assessment of the following entities:

- White coat hypertension/white coat effect
- Masked hypertension
- Postural hypotension
- Postural hypertension
- Nocturnal hypertension (can only be assessed via this tool)



## 7.0 Risk of elevated BP:

Increasing BP is associated with increasing risks for CVD, beginning at levels well within the so-called “normal” range. The Prospective Studies Collaboration, a pooling study of around 1,000,000 men and women in a number of large epidemiologic cohorts, and including data on more than 56,000 decedents, demonstrated that risks for CVD death increase steadily beginning at least at levels as low as an SBP of 115 mm Hg and DBP of 75 mm Hg. When considered in isolation, for each 20 mm Hg higher SBP and each 10 mm Hg higher DBP, there is approximately a doubling of risk for stroke death and ischemic heart disease death for both men and women [14].

### 7.1 Treatment threshold and target values:

#### 7.1.1 Optimal systolic BP target:

Data on optimal BP treatment targets, particularly for systolic blood pressure, were largely based on metaanalyses and Cochrane reviews. Individuals with mildly elevated blood pressures, but no previous cardiovascular events, make up the majority of those considered for and receiving antihypertensive therapy. Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs. Treatment caused 9% of patients to discontinue treatment due to adverse effects. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms [15].

Another meta-analysis included patients without CVD with BP in the grade 1 hypertension range (140 to 159/90 to 99 mm Hg) who were randomly assigned to an active (antihypertensive drug or more intensive regimen) or control (placebo or less intensive regimen) blood pressure-lowering regimen. It was concluded that BP reductions and numbers of events were small. BP lowering therapy is likely to prevent stroke and death in patients with uncomplicated grade 1 hypertension [16].

#### 7.1.2 Addressing the lower BP targets:

HOPE 3 trial: [17]

This trial enrolled 12,705 patients, 46% females with 65.8 years mean age, 15% of the study population was South Asians. Included were men  $\geq 55$  years, women  $\geq 65$  year with at least one of the following CV risk factors for men and two for women:

1. Elevated waist-to-hip ratio
2. History of a low level of high-density lipoprotein cholesterol
3. Current or recent tobacco use, dysglycemia
4. Family history of premature coronary disease
5. Mild renal dysfunction



The baseline BP was 138.1/81.9 mmHg and the BP decrease was 6/3 mmHg. A fixed-dose combination of candesartan 16 mg and HCTZ 12.5 mg daily was not found to be superior to placebo in reducing CV events. There were three pre-specified hypothesis-based subgroups. Participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg), who were in the active-treatment group had significantly lower rates of the first and second co-primary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes). Hope 3 demonstrated that the benefit was seen in the upper third of the SBP.

### 7.1.3 The SPRINT trial and its implications in the setting of lower goals: [18]

The SPRINT trial showed that intensive BP control to SBP <120 mm Hg results in significant cardiovascular benefit in high-risk patients with hypertension compared with routine BP control to <140 mm Hg. The goal of the trial was to compare the safety and efficacy of intensive lowering of systolic blood pressure (SBP) to <120 mm Hg versus routine management to <140 mm Hg. Patients were randomized to intensive SBP lowering (target <120 mm Hg) or routine SBP management (target <140 mm Hg). Total patients were 9,361; duration of follow-up was 5 years (median 3.26 years). Included were age  $\geq$ 50 years with hypertension with SBP  $\geq$ 130 mm Hg and at least one risk factor for heart disease:

- Presence of clinical or subclinical cardiovascular disease other than stroke
- Chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) 20-59 ml/min/1.73 m<sup>2</sup>
- A Framingham Risk Score for 10-year cardiovascular disease risk  $\geq$ 15%
- Age >75 years

The trial was terminated early due to overwhelming evidence of benefit. The primary outcome, myocardial infarction (MI), acute coronary syndrome (ACS), stroke, congestive heart failure (CHF), or cardiovascular (CV) death, was significantly lowered in the intensive BP management arm compared with the routine management arm (5.2% vs. 6.8%, hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.89; p < 0.0001).

The results of this landmark trial indicate that intensive BP lowering to a target <120 mm Hg is superior to routine management with a target of <140 mm Hg in high-risk non-diabetic patients with hypertension, including in elderly patients. There were also reductions noted in CV and all-cause mortality, accompanied by a reduction in CHF. An intensive strategy also reduced the risk of developing LVH among patients without baseline LVH and resulted in greater LVH regression among those with evidence of baseline LVH. An intensive strategy carried a higher risk of hypotension, syncope, and accelerated reductions in GFR (only in patients without CKD at baseline). This is a landmark trial and is likely to result in a paradigm shift in the management of patients with hypertension.

### 7.1.4 Assessment of BP in the SPRINT trial:

The BP was measured according to a study method called “research grade BP measurement”. SPRINT specified a 5 minutes period of seated rest in a quiet room, followed by 3 oscillometric measurements without an observer in the room. The relationship of this research-grade methodology to routine BP measurements is not known [19].





Agarwal showed that among 275 people with CKD who had BP <140/90 mm Hg when they came to the clinic; they measured BP as in SPRINT and recorded BP on the same day without specification of seated rest. Compared with routine measurement, the research-grade systolic BP was 12.7 mm Hg lower with wide limits of agreement (-46.1 to 20.7 mm Hg). Research grade systolic BP was 7.9 mm Hg lower than daytime ambulatory systolic BP and had wide agreement limits (-33.2 to 17.4 mm Hg). Whereas the routine, research-grade, and daytime ambulatory systolic BP were all related to echocardiographic LVH, the strength of the relationship between research-grade and daytime ambulatory systolic BP to left ventricular hypertrophy was similar and stronger than the strength of the relationship between routine systolic BP and LVH. It was concluded that translation of the SPRINT results would require measurement of BP as performed in that trial. Instead of an algebraic manipulation of routine clinic measurements, the SPRINT methodology of BP measurement would be needed at minimum if implementation of the SPRINT results were to be deployed in the population at large [19].

#### **7.1.5 BP target of <150/90 for ages >60 years or 80 years:**

The JNC 8 guideline suggest a target of <150/90 for age >60 years, whereas this target is used by the NICE guidelines for age 80 years or above. This evidence comes from multiple trials, which include HYVET [20], Syst-Eur [21], SHEP [22], JATOS [23], VALISH [24], and Cardio-Sis [25] trials. Moderate to high quality evidence that treating the general population aged  $\geq 60$  years with high BP to a goal < 150/90 mm Hg reduces stroke, heart failure, and coronary heart disease. Low-quality evidence shows that a systolic BP goal of < 140 mm Hg in this age group provides no additional benefit versus a higher goal of systolic BP 140 to < 160 mm Hg (JATOS) or 140–149 mm Hg (VALISH). The ages of the populations were  $\geq 80$  years in HYVET, 70–< 85 years in VALISH, 65–85 years in JATOS,  $\geq 60$  years in SHEP and Syst-Eur, and  $\geq 55$  years in Cardio-Sis. The mean BP measurements achieved in the active and/or more intensive treatment groups of these studies were 143.5/77.9 mm Hg, 136.6/74.8 mm Hg, 135.9/74.8 mm Hg, 143/68 mm Hg, 150.8/78.5 mm Hg, and 136/79.2 mm Hg, respectively. The JATOS and VALISH studies were statistically underpowered to detect such a benefit due to the very low rates of stroke and CHD reported during follow-up. The majority of these trials suggest that a systolic BP goal of < 140 mm Hg is safe in non-frail, relatively healthy older patients. In the FEVER Trial [26] there were 9,711 Chinese patients aged 50–79 years. A difference in systolic/diastolic BP as small as 4/2 mm Hg (induced by adding low-dose felodipine to low-dose hydrochlorothiazide in the trial) is associated with significant reductions in the incidence of stroke, all CVD, CHD, heart failure, and total mortality. The mean BP achieved at study end (60 months) with the addition of felodipine was 138.1/82.3 mm Hg versus 141.6/83.9 mm Hg with the addition of a placebo. A subgroup analysis for patients aged > 65 years showed a 44% reduction in all strokes [27]. Therefore it is recommended that only people over the age of 80 years should have 150/90 mmHg or less. as target.



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## 8.0 Diagnosis of hypertension:

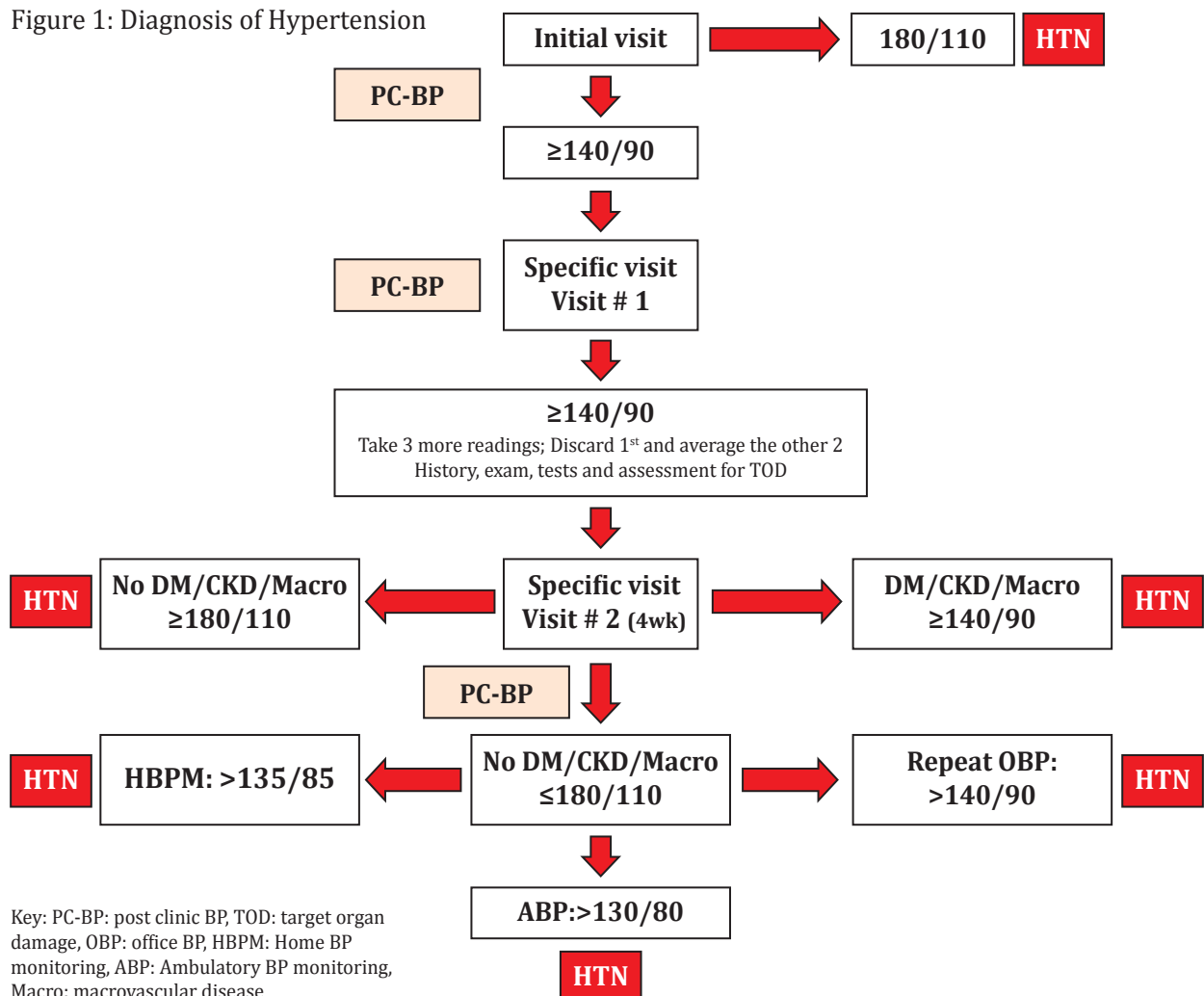
PHL endorses Hypertension Canada's [1] diagnostic approach and proposes the algorithm. [Figure 1]

- Initial visit: If SBP is  $\geq 140$  mmHg and/or DBP is  $\geq 90$  mmHg, a specific visit should be scheduled. If BP is high-normal (SBP 130 – 139 mmHg and/or DBP 85 – 89 mmHg), annual follow-up. If BP  $> 180/110$  mmHg diagnose hypertension.



- Visit 1: If SBP is >140 mmHg and/or DBP is >90 mmHg on the first reading, at least two more readings should be taken during the same visit using a validated device. The 1st reading should be discarded and the two other readings are averaged. Take a history, perform a physical examination, and assess for T.O.D. Initial tests should be ordered on this visit.
- Visit 2 (4 weeks): If there is macrovascular disease, DM and/or CKD, and BP SBP is >140 mmHg and/or DBP is >90 mmHg then diagnose HTN. If no macrovascular disease, DM and/or CKD, and BP SBP is >180 mmHg and/or DBP is >110 mmHg then diagnose HTN. If no macrovascular disease, DM and/or CKD, and BP SBP is <180 mmHg and/or DBP is <110 mmHg then evaluate further on a subsequent visit for Office BP, HBPM or ABP.
- Repeat Office BP: If the average of 3 readings of BP >160/110, or BP >140/90 averaged across 5 visits diagnose HTN.
- Home BP: If the SBP is  $\geq 135$  mmHg or the DBP is  $\geq 85$  mmHg diagnose HTN. If the average home BP is < 135/85 mmHg, it is advisable to either repeat home monitoring to confirm or perform ABP to see if BP <130/80 mean awake ABP <135/85.
- ABP: If BP >130/80 (overall), >135/85 (daytime).

Figure 1: Diagnosis of Hypertension



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## 9.0 Diagnostic work-up: [1]

Laboratory measurements should be obtained for all patients with a new diagnosis of hypertension to facilitate CVD risk factor profiling, establish a baseline for medication use, and screen for secondary causes of hypertension. (table 2). Optional tests may provide information on TOD. Further monitoring may help guide therapy or help assess secondary causes of HTN. Additional tests may be called for if there is increased hypertension severity, poor response to standard treatment approaches, a disproportionate severity of TOD for the level of BP, or historical or clinical clues that support a secondary cause. For resistant or difficult to treat hypertension a referral to a specialist is recommended.

Table 2. Diagnostic work-up needed for HTN

No.	Tests	
1	Complete blood count	<u>Basic tests:</u> Needed for baseline assessment and for CVD risk profiling
2	Fasting blood sugar	
3	Serum creatinine with eGFR	
4	Sodium, Potassium	
5	Lipid profile	
6	Urine detailed report	
7	Electrocardiogram (ECG)	
<b>Additional tests:</b>		
1	Thyroid stimulating hormone (TSH)	<u>Additional test:</u> In difficult to control BP situations
2	Echocardiogram	
3	Urine albumin creatinine ratio	
4	Uric acid	

The eGFR to be calculated as per the CKD EPI Pak equation.  
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## 9.1 Target organ damage: [table 3]

Hypertension is a major cause of cardiovascular disease and was recently put forward as the leading risk factor for global disease burden [2]. Long-term hypertension induces damage to the vasculature and myocardium, [3] as well as to the kidneys [4]. The principal focus is on the arterial vessel as the main organ involved in hypertensive patients. The heart disease might be considered as one of the principal consequences of vascular dysfunction discussed extensively in literature [5].



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Table 3. Target organ damage (TOD)

System	Complication
Cerebrovascular disease	Transient ischemic attack Ischemic or hemorrhagic stroke vascular dementia
Eye	Hypertensive retinopathy
Heart muscle	Left ventricular dysfunction and hypertrophy
Coronary artery disease	Myocardial infarction Angina pectoris Congestive heart failure
Kidney	Hypertensive nephropathy (eGFR <60ml/min/1.732)* Albuminuria
Arteries (peripheral arterial disease)	Intermittent claudication Ankle brachial index <0.9#

Adapted From CHEF 2011 guidelines. Hypertension Canada.

\*The eGFR to be calculated as per the CKD EPI Pak equation. Jessani S, et al. *Am J Kidney Dis* 2014;1:49-58.

#The Ankle Brachial Index (ABI): SBP at the ankle, divided by the SBP at the arm. (normal value 1.0 - 1.4).

ABI is independent of traditional CV risk factors.

Recommendation: Measure ABI in every smoker over 50year old, every diabetic over 50, and all patients over 70.

## 10.0 Why treat blood pressure?

Lowering BP with drug therapy provides benefit. Although when there is no target organ damage or cardiovascular risk factors and mild hypertension the benefit is not that clear but as risk factors are added to the history benefits are noted in terms of prevention of stroke and death [1, 2]. The HOPE 3 trial tested BP lowering in upper normal ranges. Although the trial did not show overall benefit the higher BP group showed significantly lower rates of first and second co-primary endpoints [3]. The benefit of treating hypertension is clear for those aged 65 years or more, diabetic patients, chronic kidney disease and for those who have a 10 years CVD risk of more than 10% [4, 5].



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## 11.0 Hypertension:

### 11.0.1 Simple hypertension (uncomplicated):

Simple or pure hypertension occurs when in the presence of sustained rise in BP above hypertension threshold, there is no compelling indication like congestive heart failure, diabetes, CAD etc. [1]. This allows for treatment to be initiated as per the treatment algorithm.

### 11.0.2 Hypertension with compelling indication: [table 4]

When HTN exists in the presence of other conditions that compel the treatment to be modified or tailored to the specific need of the disease condition as per the evidence base [1]. Example: in the post myocardial infarction state beta-blocker may be initiated as 1st line therapy, which is contrary to the simple hypertension protocol. Similarly for CHF, BB may be the choice of drug to control hypertension as it provides mortality benefit to this subgroup of HTN patients.

Table 4. Drug choices for HTN with compelling indications(initial therapy)

Conditions		Drugs
1	Heart failure	<ul style="list-style-type: none"> <li>• Diuretics</li> <li>• Beta blockers</li> <li>• ACE inhibitors/angiotensin receptor blockers</li> <li>• Aldosterone antagonist</li> </ul>
2	Myocardial infarction	<ul style="list-style-type: none"> <li>• Beta blockers</li> <li>• ACE inhibitors</li> </ul>
3	Diabetes Mellitus	<ul style="list-style-type: none"> <li>• ACE inhibitors/Angiotensin receptor blockers</li> </ul>
4	Chronic kidney disease	<ul style="list-style-type: none"> <li>• ACE inhibitors/Angiotensin receptor blockers</li> </ul>

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint National committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003 Dec. 42(6):1206-52.



### 11.1 Threshold for diagnosis and treatment:

The JNC 8, ESC, BHS, CHEP and other international guidelines [table 5] have up till now recommended <140/90 mmHg as threshold for treatment. As stated earlier, it has been known that the risk of adverse outcomes goes up as the SBP rises above 115 mmHg [2,3]. The SPRINT trial [4] showed that lowering BP to tight control <120/80 mmHg accrued benefit for the patient, although at an increased cost of myriad side effects. The AHA 2017 guidelines [5] have lowered the threshold for diagnosis to 130/80 mmHg. This reading is however more than the threshold of the SPRINT trial, which is the basis for this evidence. The SPRINT trial method of BP measurement was called the research-grade BP measurement and required 5 minutes of seated rest in a quiet room. An automated digital machine took the BP, after the research/health staff ensured the correct application of the cuff and ability of the machine to take a correct BP reading. After that three readings were taken and averaged out [4]. It was noted that this measurement of BP was not the same as office BP measurement in the clinic. It was more similar to out of clinic BP measurement, and would not be reliably reproduced in a real world scenario. A post-hoc analysis of the SPRINT trial showed that there was no significant difference between attended or unattended BP. Bauer et al, [6] showed that unattended and attended office BP measurements achieve comparable results, if measurements take place at a familiar general practitioner's office. On the contrary, Agarwal [7] showed through a prospective trial that where the routine BP, mean day time ABP and research grade BP (SPRINT protocol) showed a relationship with echocardiographic LVH, the strength of the relationship was stronger between mean daytime ABP and research grade BP than with office BP. They recommended that to accrue the same benefit. BP had to be measured as per the SPRINT protocol.

Table 5a. International Hypertension Guidelines: Classification of Hypertension

Stage	BP values	JNC 7/8	ESC	BHS	CHEP	AHA 17
Optimal	<120/80	Normal	Optimal	Optimal	Normal	Normal
Normal	120-129/80-84	Pre-HTN	Normal	Normal	Pre-HTN	Elevated
High normal	130-139/85-89	Pre-HTN	High normal	High normal	Pre-HTN	Stage I
Grade I/Stage I	140-159/90-99	Stage 1	Grade 1	Grade 1	Stage 1	Stage II
Grade II/Stage II	160-179/100-109	Stage 2	Grade 2	Grade 2	Stage 2	Stage II
Grade III/Stage III	>180/>120	Stage 2	Grade 3	Grade 3	Stage 2	Stage II
HTN crises symptoms and/or TOD	>180/110	HTN crises	Grade 3	Grade 3	HTN crises	HTN crises >180/120





Table 5b. Classification, lifestyle modification and therapy

Stage	BP values	Lifestyle Modification	Follow up	Drug Rx
Optimal	<120/80mmHg	Step 0	Follow-up 2 years	None
Elevated	120-129/80-84 mmHg	Step 1 then step 2	Follow-up 1 year	None
Pre-HTN	130-139/85-89 mmHg	Step 1 and 2 together	Follow-up 1 year if no CV risk or CVD	None
Pre-HTN	130-139/85-89 mmHg	Step 1 and 2 together	Follow-up 6 months if 10 year CV risk of CVD>10%or CVD	1 drug Rx
Stage I	140-159/90-99 mmHg	Step 1 and 2 together	Follow-up 4 - 6 weeks	1 drug Rx
Stage II	160-179/100-110 mmHg	Step 1 and 2 together	Follow-up 4 - 6 weeks	2 Drug Rx
Stage III	>180/120mmHg No TOD	Step 1 and 2 together	Follow-up 4 - 6 weeks	2 Drug Rx
HTN crises	>180/120 mmHg and TOD/Acute injury	Step 1 and 2 together	Follow-up 4 - 6 weeks	Escalate Rx

### 11.1.1 Should tight control be for every one?

Is there a J curve to BP lowering? A post hoc analysis of the SPRINT trial showed that there were 480 subjects, who had a SBP of 160 mmHg or more. The group's median 10-year Framingham risk score was  $\leq 31.3\%$ . Within this group, after adjustment for age and sex, those who were randomized to the aggressive treatment arm had almost triple the risk of death from any cause compared to those treated less intensively (4.9% vs 1.7%, hazard ratio [HR] 3.12, [95% CI 1.00-9.69];  $p=0.012$ ), although the results barely reached statistical significance [8].

The currently ongoing SHOT trial might provide more evidence on this issue for fatal and nonfatal stroke and probably also for other clinical outcome [9]. However, the optimal BP might be different between individuals and across outcomes. Indeed, 120 mm Hg of systolic BP compared to 140 mm Hg might prevent stroke in diabetic patients [10] and heart failure in non-diabetic patients [11]. However, it is probably too naive to attempt to find a universal optimal blood pressure level for all patients. The guidelines allow a framework and different targets for tailoring the therapy to the baseline BP, risk threshold and also the ability of the health infrastructure to provide care for gradual tight control in a safe manner.



11.1.2 PHL recommendation: [table 5 and figure 2]

- The PHL taking the above into account sets 130/80 as a secondary target and BP <140/90 as the primary target for treatment.
- Treatment groups to be divided into two groups.
  - o Group 1 is with no CVD, DM or CKD or 10 year risk of CVD<10%
  - o Group 2 has CVD, DM, CKD or 10 year risk of CVD >10%.
- Group 1 would be subjected to heart healthy life style modification. On the other hand group 2 would be given lifestyle modification, but if not controlled in 6 months would be started on 1 drug –medical therapy.
- The target would be primary target <140/90 mmHg, secondary BP target <130/80 mmHg.
- For all other categories (see table), if the patient has at least one risk factor the target of BP lowering should be < 130/80 mmHg.
- For those with hypertension and no other risk factor a target of < 140/90 mmHg.
- For those who are very elderly (age >80 years) the target would be <150/90 mmHg.

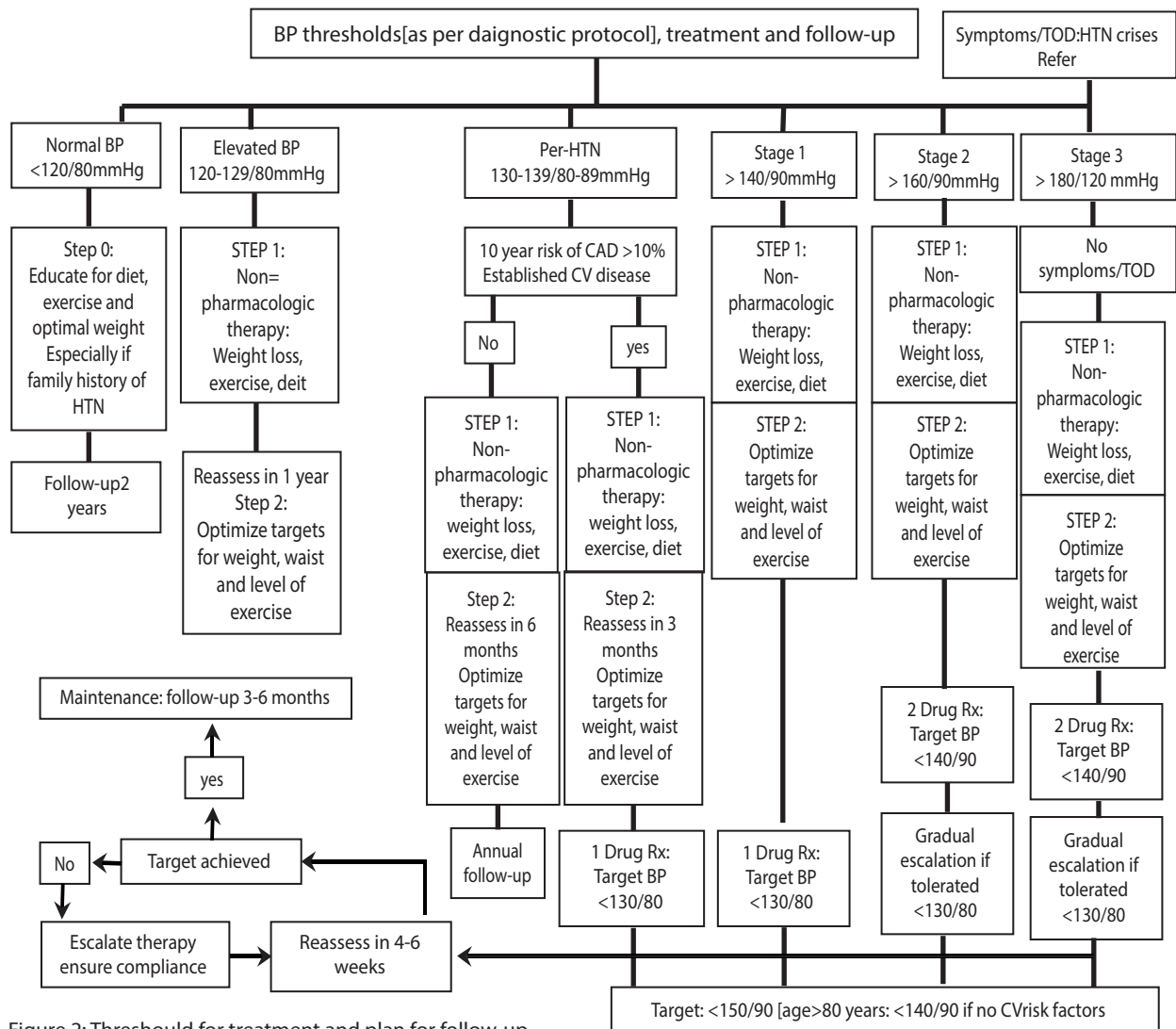


Figure 2: Threshold for treatment and plan for follow-up





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## 12.0 Global risk assessment:

The aim is to look at HTN not as an isolated disease but as part of the metabolic syndrome. Furthermore the aim is to prevent the development of atherosclerotic cardiovascular disease, which now included stroke. The PHL endorses the ACC/AHA guidelines [1] for the assessment of cardiovascular risk.

- The focus is primarily on the 10-year risk of atherosclerosis related events; the secondary focus is on the assessment of lifetime risk for adults aged 59 or younger without high shorter-term risk



- The strongest predictors of 10-year risk are identified as age, sex, race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), BP, HTN treatment status, DM, and current smoking status
- Statin therapy recommended in individuals whose 10-year atherosclerotic cardiovascular disease event risk is 7.5% or greater

**12.1 Risk calculator:** A risk calculator [2] for estimating the 10-year risk of developing a first CV event is used. The CV event is defined as a nonfatal myocardial infarction, death from coronary heart disease (CHD), or stroke (fatal or nonfatal) in a person who was initially free from ASCVD. The calculator incorporates the following risk factors:

- Sex
- Age
- Race
- Total cholesterol
- HDL cholesterol
- Systolic BP
- Treatment for HTN
- DM
- Smoking

### 12.2 Recommendations:

- For patients 20-79 years of age who do not have existing clinical CV disease, clinical risk factors assessment is recommended every 4-6 years.
- For patients with low 10-year risk (< 7.5%), assessing 30-year or lifetime risk is recommended in patients 20-59 years old.
- For patients with elevated 10-year risk, clinicians should recommend diet control, heart healthy lifestyle and statin therapy.

### 12.3 Implications of risk calculation:

The AHA/ACC score deals more with the Caucasian population so one can look at other scores like the INTERHEART score [3], which was developed based on data from 52 countries around the world. It showed that the INTERHEART risk score, based on nine easily measureable and potentially modifiable risk factors, is associated with more than 90% of the likelihood to accurately predict an acute MI, these results being consistent across all geographic regions and ethnic groups of the world, men and women, and young and old. More recently, McGorrian et al. [4]. modified the INTERHEART risk score into the INTERHEART Modifiable Risk Score (IHMRs), of which four risk score models were derived. Of these, the 'non-laboratory-based' score [4], which does not include any lab-based measures of lipid profile, can be used in primary care settings especially in resource-poor countries where there is lack of laboratories [5]. The Framingham risk score for CVD is also good for South Asian population [6]. It is important to be familiar with the risk score that one uses and all can be accessed as applications for cell phones or computers.



### 13.0 Role of ASA for the primary prevention of CV disease:

Although aspirin has a well-established role in preventing adverse events in patients with known cardiovascular disease (CVD), its benefit in patients without a history of CVD remains under scrutiny. Current data have provided insight into the risks of aspirin use, particularly bleeding, compared with its benefits in primary CVD prevention. Although aspirin is inexpensive and widely available, especially in developing countries like Pakistan, there is lack of evidence that the benefits outweigh the adverse events with continuous aspirin use in primary CVD prevention. Therefore, the decision to initiate aspirin therapy should be an individual clinical judgment that weighs the absolute benefit in reducing the risk of a first cardiovascular event against the absolute risk of major bleeding, and tailored to the patient's CVD risk [7].

Although there is evidence that aspirin is beneficial in secondary CVD prevention [8,9], findings from clinical trials and meta-analyses on aspirin benefit in primary CVD prevention are not homogenous. Since bleeding risk appears in trials to be strongly related to the ischemic risk, the benefit of aspirin is overshadowed by the bleeding hazard. Aspirin may be used for hypertensive patients with a high risk for CV disease but this needs to be tailored to the need of the patient and the patient needs to understand the reality of bleeding risk. The Multi-Ethnic Study of Atherosclerosis that involved 4229 participants who were not on aspirin at baseline and were free of diabetes mellitus revealed that participants with significant plaque in their arteries (i.e., coronary artery calcium (CAC) score  $\geq 100$ ) were estimated to be 2 to 4 times more prone to prevent a heart attack with aspirin use than to have a major bleed secondary to aspirin [10]. Adults aged 50 to 59 years with a  $> 10\%$ , 10 year CVD risk will benefit from ASA use. For ages  $< 50$  and  $> 70$  the use is not recommended. For age bracket 60 to 69 the decision has to be weighed against the bleeding risk [11].

**13.0.1 Recommendation:** Therefore, it is recommended that Aspirin use be considered only for established CV disease or patients at high risk for CV disease as estimated through a risk calculator ( $> 10\%$ , 10 year CVD risk).

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## 14.0 Role of statin therapy:

The PHL endorses the US preventive task force recommendation [1,2] for the use of:

- Low to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater.
- Selectively offer low-to moderate-dose statins to adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 7.5% to 10%.
- For the very elderly > 75 years, there are insufficient data to assess the balance of benefits and harms of initiating statin.

## 15.0 Life style modification: [table 6]

### 15.1 Body Mass Index and Waist Circumference:

The cut-off points are different for the South Asian population and therefore the WHO recommends a cut off of waist circumference of < 90 cm for men and < 80 cm for women. Cut-off points chosen vary considerably between countries; also, the variation is greater for waist circumference than for waist-hip ratio. The cut-off points appear to be chosen based on disease risk (e.g. CVD, type 2 diabetes and risk factors of CVD) and on hard outcomes such as mortality. [3,4] Data from China indicate that the prevalence of hypertension, diabetes, dyslipidemia, and clustering of risk factors all increased with increasing BMIs even at indices below the international current cut-off point for overweight (i.e. 25 kg/m<sup>2</sup>).



The Asian populations have more body fat at lower BMIs. Therefore, the cut off has been lowered. [5] For many Asian populations, additional trigger points for public health action were identified as 23 kg/m<sup>2</sup> or higher, representing increased risk, and 27.5 kg/m<sup>2</sup> or higher as representing high risk. The suggested categories are as follows: less than 18.5 kg/m<sup>2</sup> underweight; 18.5–23 kg/m<sup>2</sup> increasing but acceptable risk; 23–27.5 kg/m<sup>2</sup> increased risk; and 27.5 kg/m<sup>2</sup> or higher high risk [6].

**Table 6. Non-pharmacologic Therapy: Stepped approach**

	Standard values	Step 0	Step 1	Step 2
		To be started before the development of HTN	To be started in elevated BP, Pre HTN and all stages	To be started in elevated BP, Pre HTN and all stages (supervised)
Waist circumference	Men: < 90 cm Women: < 80 cm	Educate	Recommend	Enforce
BMI	<18.5 kg/m <sup>2</sup> [underweight] 18.5 - 23 kg/m <sup>2</sup> [normal] 23-27.5 kg/m [increased risk] >27.5 [high risk]	Educate	Recommend	Enforce
Diet DASH	Fruits, vegetables, fish, low fat dairy products	Educate	Recommend	Enforce
DASH weight reduction	To optimize weight for metabolic syndrome, DM, dyslipidemia patients	Educate	Recommend	Enforce
Salt	<100mmol/d, 2.4g Na <sup>+</sup> , 6gm NaCl	Educate	Recommend	Enforce
Exercise	Aerobic exercise for 30 mins most days/week	Educate (home training)	Recommend (training advice)	Enforce ( supervised program)
Sleep	> 6 hours	Educate	Recommend	Enforce ( sleep specialist)
Stress/Anxiety	Avoid /manage stress	Educate	Recommend	Enforce
Smoking	Quit	Quit	Quit/alternatives	Smoking cessation program
Alcohol	Quit	Quit	Quit	Quit

Note: Sedentary behavior is a person who takes less than 5000 steps in a 24-hour period. (Sports Med. 2004;34(1):1-8)

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### 15.2 Exercise: [table 6 and 7]

Aerobic exercise is universally recommended as initial lifestyle therapy for individuals with hypertension because it lowers BP 5–7 mmHg among adults with hypertension. A combination of 30 min or more per day of moderate intensity aerobic exercise on most, preferably all, days of the week and dynamic resistance exercise 2 to 3 days per week to total 150 min or more of exercise per week. The notable emphasis comes in on the inclusion of dynamic resistance exercise in combination with aerobic exercise [1]. The BP lowering effects of exercise are most pronounced in people with HTN who engage in endurance exercise with BP decreasing approximately 5–7 mm Hg after an isolated exercise session (acute) or following exercise training (chronic). Moreover, BP is reduced for up to 22 h after an endurance exercise bout (e.g., post exercise hypotension), with the greatest decreases among those with the highest baseline BP. Individuals with controlled HTN and no CVD or renal complications may participate in an exercise program or competitive athletics, but should be evaluated, treated, and monitored closely. Comorbid conditions such as diabetes, ischemic heart disease, and heart failure should be adequately controlled before the start of exercise training. While formal evaluation and management are taking place, it is reasonable for the majority of patients to begin moderate intensity exercise training (40 to less than 60%  $V\cdot O_2R$ ) such as walking. When pharmacologic therapy is indicated in physically active people it should, ideally: a) lower BP at rest and during exertion; b) decrease total peripheral resistance; and, c) not adversely affect exercise capacity. For these reasons, angiotensin converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers in case of ACE inhibitor intolerance) and calcium channel blockers are currently the drugs of choice for recreational exercisers and athletes who have HTN [2].

Exercise remains a cornerstone therapy for the primary prevention, treatment, and control of HTN. The optimal training frequency, intensity, time, and type (FITT) need to be better defined to optimize the BP lowering capacities of exercise, particularly in children, women and older adults. Based upon the current evidence, the following exercise prescription is recommended for those with high BP:

- Frequency: on most, preferably all, days of the week
- Intensity: moderate-intensity (40-< 60% of  $V\cdot O_2R$ )
- Time:  $\geq$  30 min of continuous or accumulated physical activity per day
- Type: primarily endurance physical activity supplemented by resistance exercise.





Table 7. Exercise capacity assessment

	Minimum cardiovascular benefit	Aerobic limit (level 1)	Anaerobic threshold (level 2)	Severe exercise (level 3)
Borg scale RPE	11 Fairly light	14 Between somewhat hard and hard	17 Very hard	18-20 Extremely hard to exhaustion
%VO <sub>2</sub> max	50%	60 - 65%	80 - 85%	> 85%
% HR max	70%	75 - 80%	90 - 92%	95 - 100%

National Council on strength and fitness.

[https://www.ncsf.org/pdf/ceu/relationship\\_between\\_percent\\_hr\\_max\\_and\\_percent\\_vo2\\_max.pdf](https://www.ncsf.org/pdf/ceu/relationship_between_percent_hr_max_and_percent_vo2_max.pdf)

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### 15.3 Complementary and Alternative Medicine:

#### Yoga:

A recent meta-analysis was conducted of 17 randomized and non-randomized trials of yoga and hypertension. [3] Results showed that yoga had a modest effect on both SBP [-4.17 mm Hg] and DBP [- 3.26 mm Hg]. There was substantial heterogeneity present across the included studies. The effects of yoga on BP varied by the type of yoga intervention and by comparison group but not by duration of yoga practice. When the analysis was restricted to studies using interventions incorporating three elements of yoga practice [postures, meditation and breathing] larger reductions of SBP and DBP [-8.17 mmHg and -6.14 mmHg] were observed. Yoga was also associated with a significant decline in SBP and DBP [-7.96 mm Hg and -5.52 mm Hg] relative to no treatment but not when compared to exercise or other intervention types [4].

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**15.4 Weight loss:** [table 8] Up to 60% of all individuals with hypertension are more than 20% overweight. The centripetal fat distribution is associated with insulin resistance and hypertension. Even modest weight loss (5%) can lead to reduction in BP and improved insulin sensitivity. Weight reduction may lower blood pressure by 5-20 mm Hg per 10 kg of weight loss in a patient whose weight is more than 10% of ideal body weight [1].



### 15.5 Salt intake: [table 8]

A moderate reduction in sodium chloride intake can lead to a small reduction in blood pressure. The literature shows that the average daily consumption of sodium chloride should not exceed 6 g; this may lower BP by 2-8 mm Hg [2,3]. The effect of sodium chloride is particularly important in individuals who are middle-aged to elderly with a family history of hypertension. [1] A low-sodium diet added to drug therapy yielded additional reductions in both BP and proteinuria, emphasizing the beneficial effect of dietary salt reduction in the management of hypertensive patients with renal insufficiency [1].

### 15.6 Smoking cessation and other tobacco use: [table 8]

Cessation of cigarette smoking constitutes the single most important preventive measure for CAD. Persons who consume more than 20 cigarettes daily have a 2- to 3-fold increase in total heart disease. Continued smoking is a major risk factor for recurrent heart attacks [4]. It is the need of the day to have smoking cessation program in hospitals where a concerted effort can be made to ensure that current smokers quit. Education at step 0, that is at a stage before the development of disease or risk factors for CV disease is essential on a large scale. Smoking is a risk factor for CVD in women and men; however, a systematic review and meta-analysis by Huxley and Woodward suggests that in some countries, smoking by women is on the rise; the study suggests that proper counseling and nicotine addiction programs should focus on young women [5].

There is association between the use of smokeless tobacco and hypertension in the general population and in diabetic patients [6]. This association is linked to the nicotine and salt content of smokeless tobacco and also to renin-aldosterone suppression due to the licorice contained in chewing tobacco (and its active ingredient, glycyrrhetic acid, which may have a causative role in tobacco chewers' hypertension [7].

### 15.7 Nutrients, vitamins and fish oil:

Controlling blood pressure down to, ideally, less than 130/80 mmHg is vital for long-term circulatory health. While medication is often needed, diet and lifestyle changes can improve BP control and help to limit the number and dose of medicines needed. It is advised to increase food items rich in vitamins and nutrients as in the DASH diet. In smaller trials and meta-analyses, the nutrients and vitamins have been shown to reduce BP compared to placebo and in addition to drug therapy [8]. Examples of Vitamin C and D; fish oil or fish intake (2 – 4 servings/week); nutrients like calcium, magnesium, potassium and items like black cumin, garlic and black chocolates. It must be stressed here that high quality data are not available [8].





Table 8: Heart Healthy Life Style

	JNC	AHA	PHL	BP reduction
Reduce weight	Maintain normal weight (BMI 18.5-24.9kg/m <sup>2</sup> )	Attain BMI <25 kg/m <sup>2</sup>	18.5-23kg/m <sup>2</sup> Waist: 90 cm men,80 cn women	5-20 mm Hg/10 kg weight loss
DASH diet	Rich in fruits, Vegetables, low fat dairy, reduced saturated and total fats	Same recommendations	Endorse DASH, plus DASH weight loss diet for overweight	8 - 14 mm Hg
Sodium intake	≤100 mmol/day (2.4g Na <sup>+</sup> . 6g NaCl)	65 mmol/d (1.5g Na <sup>+</sup> . 3.8g NaCl)	≤100 mmol/day (2.4g Na <sup>+</sup> , 6g NaCl)	2 - 8 mm Hg
Physical activity	Regular aerobic exercise for 30 minutes most days of the week	None given	30 mins,moderate-intensity aerobic activity /5 days per week (total of 150) <b>OR</b> 25 minutes of vigorous aerobic activity x 3d/wk (total of 75 minutes); or a Combination of moderate- and vigorous-intensity aerobic activity <b>AND</b> Moderate to high Intensity muscle-strengthening activity 2 /wk for additional health benefits <b>For BP lowering:</b> 40 mins of moderate to vigorous exercise 3-4 times/wk	4 - 9 mm Hg
Stress	None given	None given	Avoid stress/manage stress	Not assessed
Potassium intake	None given	120 mmol/day	120mmol/day	variable
Alcohol	≤2drinks/d for men; ≤1 drink/d for women	same	No alcohol	2 – 4 mm (if alcohol reduced)

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## 16.0 Drugs to treat hypertension: [table 9a and 9b]

Multiple drug classes (see table) are available as mainstream and evidence based choices. These include the ACE inhibitors (ACEI), angiotensin blockers (ARB), calcium channel blockers (CCB), diuretics (thiazide, thiazide type), Aldosterone antagonists (AA), alpha blockers (AB) and beta blockers (BB). The other less used ones are hydralazine, clonidine, methyl dopa etc. For rapid lowering of BP drug administration for hypertensive emergencies requires intravenous administration, nitroprusside, hydralazine, glyceryl trinitrate (GTN), esmolol etc. [1,2].

Table 9a. Drugs for treatment of hypertension (A-C-D-S)

Class	drug	Dose (mg)	Frequency/day	Comments
ACE inhibitors (ACEI) <b>A</b>	Captopril	12.5 – 150	2 or 3	Increased risk of hyperkalemia, especially in patients with CKD or in those on K+ supplements or K+-sparing drugs. There is a risk of AKI in patients with severe bilateral renal artery stenosis. Do not use if patient has history of angioedema with ACE inhibitors. Avoid in pregnancy.
	Enalapril	5 – 40	1 or 2	
	Fosinopril	10 – 40	1	
	Lisinopril	10 – 40	1	
	Perindopril	4 - 16	1	
	Quinapril	10 – 80	1 or 2	
	Ramipril	2.5- 10	1 or 2	
Angiotensin Receptor Blockers (ARB) <b>A</b>	Candesartan	8 – 32	1	Same as for ACEI Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued.
	Irbesartan	150 -300	1	
	Losartan	50 – 100	1 or 2	
	Olmesartan	20 – 40	1	
	Telmisartan Valsartan	20 - 80	1	
Calcium channel blockers Dihydropyridines <b>C</b>	Amlodipine	2.5 -10	1	Avoid use in HFrEF; amlodipine or felodipine may be used if required. Associated with dose-related pedal edema, which is more common in women than men.
	Felodipine	5 – 10	1	
	Nicardipine SR	5 – 20	1	
	Nifedipine LA	60 - 120	1	
Calcium channel blockers Non-Dihydropyridines <b>C</b>	Diltiazem	180 – 360	3	Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. Do not use in patients with HFrEF. There are drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor).
	Diltiazem SR	180 – 360	2	
	Verapamil	120 – 480	3	
	Verapamil SR	240 – 480	1	
Thiazide or thiazide type diuretics <b>D</b>	Hydrochlorothiazide	12.5 – 50	1	Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. Avoid in gout
	Chlorthalidone	12.5 – 25	1	
	Indapamide	1.25 – 1.5	1	
	Metolazone	2.5 - 10	1	
Aldosterone antagonis <b>S</b>	Spironolactone (Eplerenone as alternative)	25 – 100	1	Preferred agents in primary aldosteronism and resistant hypertension. Gynecomastia and impotence Avoid use with K+ supplements, other K+-sparing diuretics, or significant renal dysfunction.

\* Cough incidence with ACE inhibitor in Pakistani Population is 7%  
( Professional Medical Journal 2016 Vol.23 Issue 9, 1145-1148 )



Table 9b. Drugs for treatment of hypertension (5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> line drugs)

Class	drug	Dose (mg)	Frequency/day	Comments
Betablockers Cardioselective	Atenolol	25 – 100	1 to 2	Beta blockers are not recommended as first-line agents unless the patient has IHD or HF. These are preferred in patients with bronchospastic airway disease requiring a beta blocker. Bisoprolol and metoprolol succinate are preferred in patients with HFrEF. Avoid abrupt cessation.
	Bisoprolol	2.5 – 10	1	
	Metoprolol tartarate	100 – 400	1 to 2	
	Metoprolol succinate	50 - 200	1	
Beta blockers— cardioselective and vasodilatory	Nebivolol	5 – 40	1	Nebivolol induces nitric oxide–induced vasodilation. Avoid abrupt cessation.
Beta blockers— noncardioselective	Nadolol	40 – 120	1	Avoid in patients with reactive airways disease. Avoid abrupt cessation.
	Propranolol IR	160 - 480	2	
Beta blockers— combined alpha- and beta-receptor	Carvedilol	12.5 – 50	2	Carvedilol is preferred in patients with HFrEF. Avoid abrupt cessation.
	Labetalol	200 – 800	2	
Alpha-1 blockers	Doxazosin	1 – 8	1	Orthostatic hypotension (older age). They may be considered with concomitant BPH.
	Prazosin	2 - 20	2 or 3	
Direct vasodilators	Hydralazine	50 - 300	3 to 4	Sodium and water retention and reflex tachycardia; use with a diuretic and beta blocker. Hydralazine is associated with drug-induced lupus- like syndrome at higher doses.

### 16.1 Algorithmic approach to the treatment of hypertension: [figure 3]

The treatment of hypertension entails an algorithmic approach as it makes it simple to follow, is universal and has a better compliance. As shown in the figure an ACD-SDB approach is recommended, which is a change from the ABCD therapy. There is robust data to suggest that ACE inhibitors are the category best suited for initiation of therapy across most age groups (including the elderly) and non-fertile females [3]. As shown in figure 3; In contrast ARB in individual trials and systematic meta-analyses have repeatedly demonstrated to significantly reduce systemic BP, stroke, and the subsequent development of heart failure and diabetes mellitus [4,5]. However, no individual trial or meta-analysis has observed an impact of ARB treatment on the incidence of myocardial infarction (MI), cardiovascular mortality, or all-cause mortality. All-cause mortality is the most comprehensive summary indicator of cardiovascular benefit of treatment [4,5] and, consequently, it is surprising that ARBs have no impact given the other clinical benefits. ACE inhibitors have been used in the elderly as well with benefit. [6, 7, 8].

However, in case of non-availability or inability to use any of the first three drugs initial drugs, the other classes can be used. It is noted as mentioned in the PHL 2009 guidelines that increasing age favors the use of diuretic and dihydropyridine CCB, where as ACEI are best for the younger age group. The control of BP to steeper targets requires use of up to three or more drugs [6], which will include the first choice ACD combination. The PATHWAY 2 trial [9] has given us the 4th to 6th line drugs in the form of spironolactone, bisoprolol and doxazosin (bisoprolol and doxazosin can be interchanged for any concomitant indication like benign enlargement of the prostate or palpitations).



### 16.2 Combination therapy: (New Onset Diabetes)

It is increasingly recognized that persons with hypertension have a high prevalence of insulin resistance and are at substantially higher risk of developing type 2 diabetes mellitus. [11,12,13] Verdecchia et al's data [14] support prior observations that certain antihypertensive drug classes (diuretics and  $\beta$ -blockers) may increase this propensity of patients with hypertension to develop type 2 diabetes [13]. In the ASCOT-BPLA trial a regimen based on a calcium channel blocker (CCB) (amlodipine), with or without addition of an angiotensin converting enzyme (ACE) inhibitor (perindopril), reduced the risk of new-onset diabetes by 34% in hypertensive patients, compared with a regimen based on a beta-blocker (atenolol) with or without a thiazide-type diuretic, bendroflumethiazide. [15] The same has been noted in other trials for diuretics as compared to ACE, ARBs and CCBs inhibitors [16, 17]. There is enough evidence to support that beta blockers and diuretics, especially when combined, have adverse metabolic effects and increase the risk of new-onset diabetes in predisposed patients. The combination of diuretics and  $\beta$ -blockers in primary prevention among people with a high risk of developing diabetes is discouraged [18].

### 16.3 Combination therapy: (free versus fixed dose combination)

Initiating fixed-dose combination (FDC) therapy with a diuretic and ACEI, ARB, or beta-adrenergic blocking agent was associated with better adherence as compared to diuretic monotherapy. Studies have shown that adherence to treatment increases with fixed-dose combinations. [19,20] Adherence to fixed-dose combination therapy of CCB with angiotensin-converting enzyme (ACE) inhibitor was significantly greater than for free combination therapy. [19] Patients receiving a once-daily, single-capsule, fixed-dose combination of ACE and CCB demonstrated better medication adherence than subjects receiving ACE and CCB as separate components. [20] Initiating fixed-dose combination (FDC) therapy with diuretic and ACE, ARB, or beta-adrenergic blocking agent was associated with better adherence as compared to diuretic monotherapy. [21] So it is recommended to try FDC as much possible and as early as possible.

### 16.4 Resistant Hypertension: [figure 3]

If the BP does not remain within normal range even after the use of maximum doses of three antihypertensive medicines, of which one is a diuretic, the condition is called resistant hypertension. We now know through the PATHWAY 2 trial [9] that true resistant hypertension is a sodium dependent phenomenon. This can be treated with the aldosterone antagonist, spironolactone, which now emerges as the 4th line therapy for hypertension.



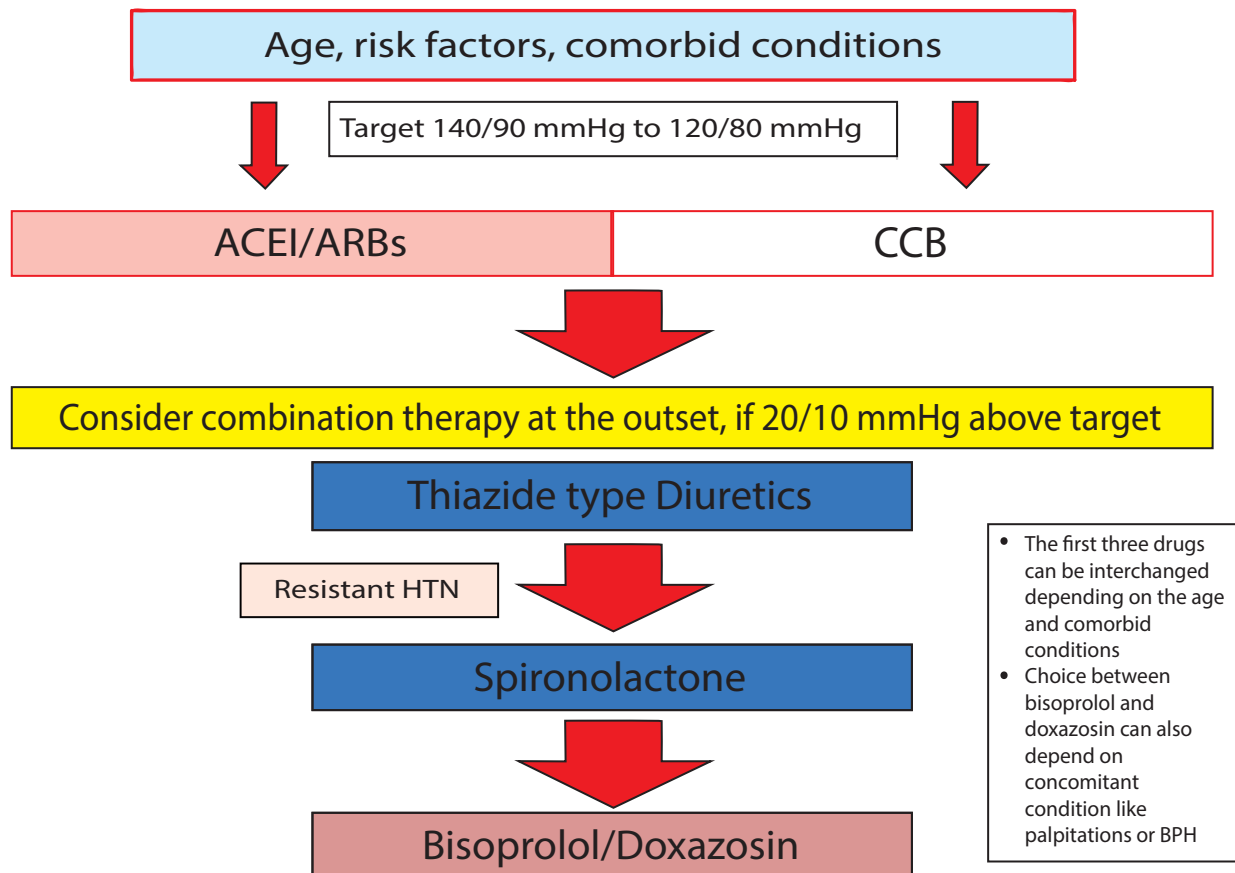


Figure 3. ACD-SBD approach

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## 17.0 White Coat Hypertension (WCH), White Coat Effect (WCE) or White Coat Syndrome (WCS):

The three terms are used interchangeably. However some authors have used the terms separately, where WCH is kept for normotensive patients and WCE is used for hypertensive patients having this condition. The PHL endorses the definition provided by the European Society of Hypertension/Society of Cardiology guidelines 2013, which describe WCH as office systolic/diastolic BP measurements of >140/90 mmHg on at least three occasions, with normal ambulatory or home BP readings (24-hour ambulatory blood pressure <130/80 mmHg or a home blood pressure reading of 135/85 mmHg) [1]. The failure to adequately diagnose white coat hypertension with standardized measurements has led to the inappropriate prescription and overuse of antihypertensive medications for individuals who are not persistently hypertensive [2]. The reported WCH overall prevalence is 13% [3]. However, a recent review reported that 30%–40% of patients who are diagnosed with hypertension on the basis of their office BP measurement alone have normal out-of-office BP, according to ABP measurements [4]. Ambulatory monitoring may be the most effective method for diagnosing and confirming whether patients are persistently hypertensive or experiencing white coat syndrome. The frequency of WCH was 16.6% in a study done in Karachi on patients undergoing ABP monitoring [5]. There is evidence that negative health outcomes, such as target organ damage, are associated with white coat hypertension. In addition, over time, white coat hypertension can progress to sustained hypertension. Changing the typical protocol for office blood pressure measurement is recommended [6]. It is recommended to follow these patients closely for the development of HTN.

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### 17.1 Masked Hypertension (MH):

The term, masked hypertension (MH) is reserved for antihypertensive naïve patients. In patients with treated hypertension, the presence of residual masked hypertension is called masked uncontrolled hypertension (MUCH).

**Definition:** For daytime measurements, the definition of masked hypertension in untreated individuals is an in-office BP of <140/90 mm Hg and an out of-office BP of  $\geq$ 135/85 mm Hg.

A meta-analysis of population adjusted for co-variables, unmasked, masked hypertension in 7.5% and 29.3% of individuals with normotension and prehypertension, respectively [1,2]. It has been recommended that a positive diagnosis of masked hypertension be confirmed by ABPM before commencing antihypertensive therapy [3,4].

Masked hypertension occur in a multitude of diverse clinical settings that on frequent occasions elevate BP more often at night than during the day but also these associated medical conditions are at high risk for future CVD events. Although HBPM may be the preferred diagnostic method of assessing out-of-office BP during the initiation and dose-titration of antihypertensive therapy, the use of ABPM will be necessary to rule out undiagnosed “nocturnal masked hypertension”. Importantly, undiagnosed and untreated masked hypertension and treated but uncontrolled masked hypertension represent 2 significant high-risk populations of public health concern. It is recommended that clinic BP measurements should be supplemented with HBPM and ABPM to address MH and MUCH [5].

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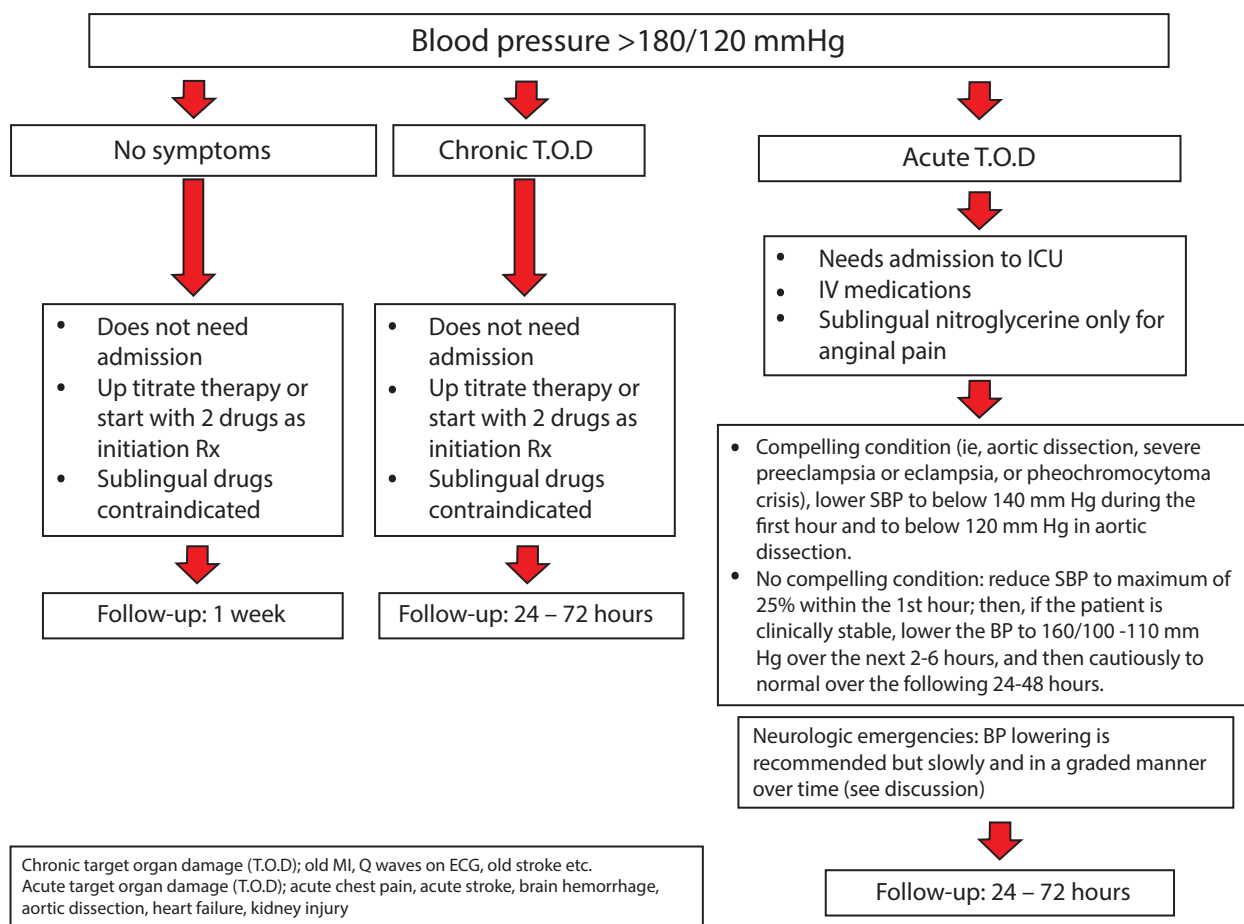


## 18.0 Hypertension crises: [1] [figure 4]

HTN crisis is characterized by a severe and abrupt increase in BP with impending or progressive acute target organ damage. The starting point of crises starts with BP levels of  $>180/120$  mmHg. The decision to treat with IV medication and admission remains with symptoms of acute target organ injury e.g ischemic chest pain, signs of stroke, renal failure etc. HTN crises can be divided into the following based on the presence or absence of acute TOD, respectively: [2]

1. Severe HTN:
2. Hypertensive urgency:
3. Hypertensive emergency:

Figure 4: Management of Hypertensive Crises



## 18.1 Severe hypertension without TOD:

When the BP is  $>180/120$  mmHg and there is no chronic target organ damage or ongoing acute target organ injury the condition is called severe hypertension.



**18.2 Hypertensive urgency:** When the BP is  $>180/120$  mmHg and there is chronic target organ damage but no ongoing acute target organ injury, the condition is called hypertensive urgency. It does not require IV medications and only need up-titration of oral medications and an early follow-up at 1 week. As mentioned in a separate section, the use of sublingual nifedipine or captopril or any other short acting antihypertensive is discouraged.

**18.3 Hypertensive Emergency:** When the BP is  $>180/120$  mmHg and there is ongoing acute target organ injury, the condition is called hypertensive emergency. It requires IV medications and the BP is brought down early but in a protocol directed graded manner. Once discharged the follow-up is early in 1 week.

Recent retrospective studies have demonstrated that emergency department referrals from an outpatient clinic or rapid BP-lowering strategies in the emergency department do not lead to improved outcomes in patients with HTN urgency [3]. HTN crises can be a de-novo manifestation or a complication of essential or secondary HTN. The presence of acute TOD is a major poor prognostic indicator. The main objectives of the management are distinction of emergency versus urgency and appropriate risk stratification, prevention or regression of acute TOD due to severely elevated BP, prevention of recurrence with an effective long-term management plan and avoidance of rapid lowering of BP except in some special circumstances. The majority of patients with asymptomatic urgency patients can be safely managed in the outpatient setting without exposing them to the risks of aggressive BP lowering. However, patients with HTN emergency require hospitalization, prompt treatment and close monitoring in the ICU setting [3].

The PHL endorses the recommendations for hypertensive crises and emergencies include the following: [2]

- Admit adults with a hypertensive emergency to an ICU for continuous monitoring of BP and target organ damage, as well as for parenteral administration of an appropriate medication.
- For adults with a compelling condition (i.e., aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), lower SBP to below 140 mm Hg during the first hour and to below 120 mm Hg in aortic dissection.
- For adults without a compelling condition, reduce the SBP to a maximum of 25% within the first hour; then, if the patient is clinically stable, lower the BP to 160/100 -110 mm Hg over the next 2-6 hours, and then cautiously to normal over the following 24-48 hours.

**18.3.1 Acute coronary syndrome:** Beta-blockers and nitroglycerin (NTG) are the preferred drugs. NTG contraindicated in the presence of phosphodiesterase inhibitors like sildenafil [3].

**18.3.2 Heart failure:** IV nitroglycerin or sublingual nitroglycerin (as it infuses 500 mcg of drug in a single dose rapidly). Treat with vasodilators (in addition to diuretics) for a SBP of 140 mm Hg [5].

**18.3.3 Aortic dissection:** In aortic dissection, the preferred medications are labetalol, nicardipine, nitroprusside (with beta-blocker), esmolol, and morphine sulfate. However, avoid beta-blockers if there is aortic valvular regurgitation or suspected cardiac tamponade. Lower the SBP to below 120 mm Hg within 20 minutes. Beta-blockers before vasodilators to avoid reflex tachycardia or inotropic effect [3].



**18.3.4 Preeclampsia/eclampsia:** The preferred medications are hydralazine, labetalol, and nicardipine. Avoid nitroprusside, ACEIs, ARBs, and renin inhibitors. The SBP should be lowered to below 140 mm Hg during the first hour [3,5]. If the platelet count is less than 100,000 cells mm<sup>3</sup>, the BP should be maintained below 150/100 mm Hg. Treat with IV magnesium sulfate to avoid seizures [6].

**18.3.5 Pheochromocytoma/cocaine toxicity:** Diazepam, phentolamine (alpha adrenergic antagonist), and nitroglycerin/nitroprusside are the preferred drugs. However, avoid beta adrenergic antagonists before administering phentolamine [7]. Lowering the SBP to below 140 mm Hg during the first hour, with phentolamine IV bolus dose of 5 mg. Additional bolus doses may be given every 10 minutes as needed to achieve target BP. Only after alpha blockade can beta-blockers be added for BP control [3].

**18.3.6 Neurologic emergencies:** BP reduction is indicated in neurologic emergencies; however, it has to be done in a gradual and graded manner. There are some exceptions as mentioned below:

- **Hypertensive encephalopathy:** Recommended to reduce the MAP 25% over 8 hours. [4] Labetalol, nicardipine, esmolol are the preferred medications; nitroprusside and hydralazine should be avoided.
- **Acute ischemic stroke:** For acute ischemic stroke immediate BP lowering is not recommended due to the Cushing effect that maintains cerebral perfusion in the acute phase. Therefore hold antihypertensive medications:
  - o Unless the SBP is above 220 mm Hg or the DBP is over 120 mm Hg
  - o Unless the patient is eligible for IV tissue plasminogen activator (tPA); then, the goal is a gradual reduction of BP with a goal SBP of less than 185 mm Hg and a DBP below 110 mm Hg before initiating thrombolytic therapy. [2] After initiating drug therapy but before administering tPA, the SBP should be maintained at less than 180 mm Hg and the DBP below 105 mm Hg for 24 hours. [3,4]
  - o The preferred medications are labetalol and nicardipine
- **Acute intracerebral hemorrhage:** For acute intracerebral hemorrhage, the preferred medications are labetalol, nicardipine, and esmolol; avoid nitroprusside and hydralazine.
  - o The treatment is based on clinical/radiographic evidence of increased intracranial pressure (ICP). If there are signs of increased ICP, maintain the MAP just below 130 mm Hg (or SBP <180 mm Hg) for the first 24 hours after onset. In patients without increased ICP, maintain the MAP below 110 mm Hg (or SBP <160 mm Hg) for the first 24 hours after symptom onset. [4]
  - o In adults with acute intracerebral hemorrhage who present with an SBP above 220 mm Hg, continuous IV drug and close BP monitoring is reasonable to lower SBP. [3] Note that it may be harmful to immediately lower SBP to below 140 mm Hg in adults with spontaneous intracerebral hemorrhage who present within 6 hours of the acute event and have an SBP between 150 and 220 mm Hg. [4]
- **Subarachnoid hemorrhage:** The preferred drugs are nicardipine, labetalol, and esmolol ; nitroprusside and hydralazine should be avoided.
  - o Maintain the SBP below 160 mm Hg until the aneurysm is treated or cerebral vasospasm occurs. Although oral nimodipine is used to prevent delayed ischemic neurologic deficits, it is NOT indicated for treating acute hypertension. [4]



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## 19.0 Pregnancy and hypertension: [1]

Hypertension in pregnancy is defined in four categories:

1. Preeclampsia/eclampsia
2. Chronic hypertension
3. Chronic hypertension with superimposed preeclampsia
4. Gestational hypertension.

**Definition of preeclampsia:** [table 10, 11] Recent definition has taken away proteinuria as mandatory for the diagnosis. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances.

- Gestational hypertension: BP elevation after 20 weeks of gestation in the absence of proteinuria or the associated systemic findings.
- Chronic hypertension: Hypertension that predates pregnancy.
- Superimposed preeclampsia: Chronic hypertension in association with preeclampsia.





Table 10: Severe features of preeclampsia

<b>Severe Features of Preeclampsia (any one of the features)</b>	
BP	BP >160 mm Hg or higher, or diastolic BP >110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
Platelets	Thrombocytopenia (platelet count less than 100,000/microliter)
Liver	Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
Kidney	Progressive renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
Pulmonary edema	Pulmonary edema
CNS/visual	New-onset cerebral or visual disturbances

Table 11: Risk factors for the development of preeclampsia

<b>High risk features of preeclampsia:</b>	
	Hypertension in a previous pregnancy
	Chronic kidney disease
	Autoimmune disease e.g. SLE, or antiphospholipid syndrome
	Type 1 or 2 diabetes
	Chronic hypertension
<b>Moderate risk features of preeclampsia</b>	
	First pregnancy, age >40 years
	Pregnancy interval of >10 years
	BMI >35 kg/m <sup>2</sup> at first visit
	Family history of preeclampsia
	Multiple pregnancy

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### 19.1 Diagnosis of HTN in pregnancy:

BP readings of  $\geq 140/90$  mmHg on two occasions 4 hours apart.  
Threshold for treatment:

- BP  $\geq 140/90$  mmHg and proteinuria
- BP  $\geq 160/110$  mmHg even without proteinuria



**19.1.1 Proteinuria:** Protein excretion of 300 mg or more in a 24-hour urine collection. Alternatively, a timed excretion that is extrapolated to this 24-hour urine value or a protein/creatinine ratio of at least 0.3 (each measured as mg/dL) is used. Because of the variability of qualitative determinations (dipstick test), this method is discouraged for diagnostic use unless other approaches are not readily available

## 19.2 Treatment of HTN in pregnancy: [figure 5, table 12a, 12b]

It is recommended to closely monitor women with gestational hypertension or preeclampsia without severe features, with serial assessment of maternal symptoms and fetal movement (daily by the woman), serial measurements of BP (twice weekly), and assessment of platelet counts and liver enzymes (weekly). For women with gestational hypertension, monitoring BP at least once weekly with proteinuria assessment in the clinic and with an additional weekly measurement of BP at home or in the office is suggested. For women with mild gestational hypertension or preeclampsia with a persistent BP of less than 160 mm Hg systolic or 110 mm Hg diastolic, it is suggested that antihypertensive medications not be administered. For women with gestational hypertension or preeclampsia without severe features, it is suggested that strict bed rest not be prescribed.

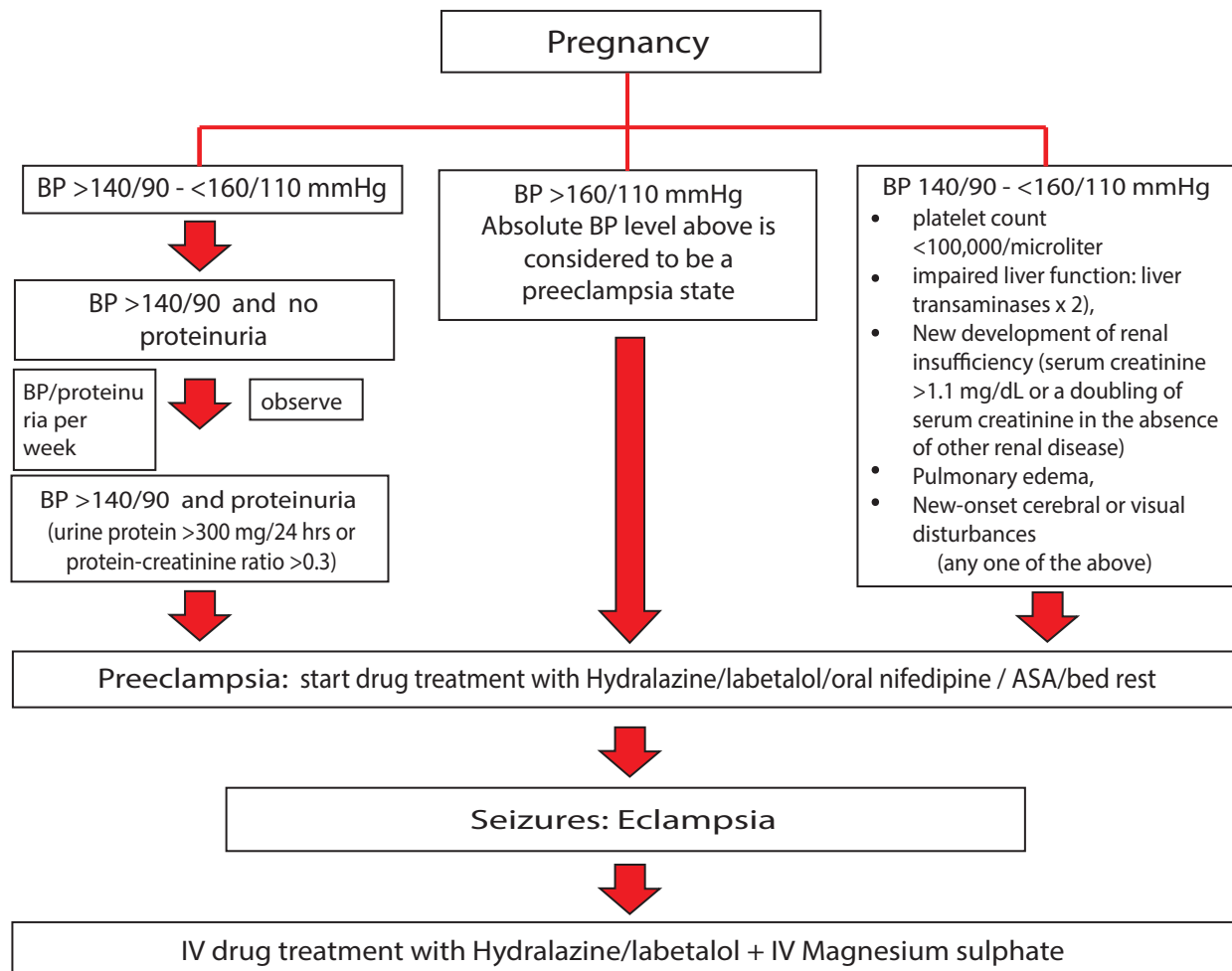


Figure 5: Algorithm for the management of hypertension



Table 12a: Drug treatment in pregnancy – first line drugs

Pregnancy: First line drugs for BP control					
Drug	Dose	FDA Class	Safety	Side Effects	Breast Feeding
<b>First line drugs</b>					
Methyldopa	0.5 to 3g/day in 2 divided doses	B	Proven safety and efficacy	Some concern with depression, Hepatic disturbances, hemolytic anemia -may not lower BP adequately	Compatible with breast milk
Labetalol	200 to 1200mg/day per oral in 2-3 divided doses 20-40mg intravenous (max 220mg total)	C	Safety similar to methyldopa may be more efficacious than methyldopa	May be associated with fetal growth restriction. Neonatal hypoglycemia with larger doses	Usually compatible with breast milk

Modified from Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. *Drugs*. 2014 Mar; 74(3): 283–296.

Table 12b: Drug treatment in pregnancy – second line drugs

Pregnancy: Second line drugs for BP control						
Drug	Dose	FDA Class	Safety	Side Effects	Breast Feeding	
Nifedipine Long-acting	10–30 mg per oral	C	Widely used	May inhibit labor; Rarely, profound hypotension if short-acting agent is used with magnesium	May inhibit labor; Rarely, profound hypotension if short-acting agent is used with magnesium	Usually compatible with breast milk
Verapamil	80mg three times a day per oral	C	Similar efficacy to other oral agents	Risk of interaction with magnesium – bradycardia	Risk of interaction with magnesium – bradycardia	Usually compatible with breast milk
Clonidine Alternative option	0.1–0.6mg/day in 2 divided doses	C	Efficacy similar to methyldopa	Safety similar to methyldopa limited data regarding fetal safety	Efficacy similar to methyldopa	Possible breast milk effects
Hydrochlorothiazide Useful in chronic hypertension	12.5–25 mg/day	B	Volume contraction, electrolyte abnormalities – rare with small doses	Volume contraction, electrolyte abnormalities – rare with small dose	Volume contraction, electrolyte abnormalities – rare with small dose	May reduce breast milk production
Hydralazine Not recommended by ESC	50–300 mg/d in 2–4 divided doses Efficacious IV agent	D	Possible maternal polyneuropathy, drug-induced lupus, neonatal lupus and thrombocytopenia; Tachyphylaxis	Possible maternal polyneuropathy, drug-induced lupus, neonatal lupus and thrombocytopenia; Tachyphylaxis	Possible maternal polyneuropathy, drug-induced lupus, neonatal lupus and thrombocytopenia; Tachyphylaxis	Usually compatible with breast milk

Modified from Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. *Drugs*. 2014 Mar; 74(3): 283–296.



### 19.3 Antihypertensive Drugs to Treat Severe Hypertension in Pregnancy: [table 12a and 12b]

The objectives of treating severe hypertension are to prevent potential cardiovascular (congestive heart failure and myocardial ischemia), renal (renal injury or failure), or cerebrovascular (ischemic or hemorrhagic stroke) complications related to uncontrolled severe hypertension. No randomized trials in pregnancy could be identified to determine the level of hypertension to treat to prevent these complications. Data from case series, as well as from developing countries where antihypertensive medications were not used in women with severe gestational hypertension or severe preeclampsia reveal increased rates of heart failure, pulmonary edema, and death. These life-threatening maternal complications justify recommending the use of medications to lower BP to a safe range even though the magnitude of this risk is unknown.

Several randomized trials compared different antihypertensive drugs in pregnancy. In these trials, parenteral hydralazine was compared with labetalol or oral nifedipine. An updated Cochrane systematic review of 35 trials that involved 3,573 women found no significant differences regarding either efficacy or safety between hydralazine and labetalol, or between hydralazine and any calcium channel blocker [2]. The results of these trials suggest that hydralazine, labetalol, or oral nifedipine can be used to treat acute severe hypertension in pregnancy as long as the medical provider is familiar with the drug to be used, including dosage, expected time of onset of action, and potential adverse effects and contraindications [2].

Theoretical concern exists that the combined use of nifedipine and magnesium sulfate can result in excessive hypotension and neuromuscular blockade. A review on the subject concluded that the combined use of these drugs does not increase such risks; however, this recommendation was based on limited data [3].

In women requiring antihypertensive medications for severe hypertension, the choice and route of administration of drugs should be based primarily on the physician's familiarity and experience, adverse effects and contraindications to the prescribed drug, local availability, and cost.

**19.3.1 Chronic hypertension:** Methyldopa, labetalol, beta blockers (other than atenolol), slow release nifedipine, and a diuretic in pre-existing hypertension are considered as appropriate treatment [4]. If a woman's blood pressure is well controlled on an agent pre-pregnancy she may continue it during pregnancy, with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. When restarting drug therapy, in women with chronic hypertension, methyldopa is recommended as first line therapy.

**19.3.2. Emergency treatment in preeclampsia:** IV hydralazine, labetalol and oral nifedipine can be used [4]. It is also recommend that methyldopa and labetalol are appropriate first-line agents and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended [5,6].



**19.3.3 Magnesium Sulphate:** In a Cochrane review of treatment of women with preeclampsia, magnesium sulphate more than halves the risk of eclampsia, and probably reduces maternal death [7].

**19.3.4 Aspirin use:** Doses up to 75 mg appear to be safe. Women at high risk (table) of preeclampsia or with more than one moderate risk factor (table) for preeclampsia may be advised to take 75mg of aspirin daily from 12 weeks until the birth of the baby, provided that they are at low risk of gastrointestinal hemorrhage [8].

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## 20.0 Hypertension in the elderly:

### 20.1 Isolated systolic hypertension:

Isolated systolic hypertension (ISH) has often been defined as a systolic blood pressure above 160 mmHg, with a diastolic blood pressure below 90 mmHg [1-3].



## 20.2 Effect of age on BP:

Data have shown that the systolic BP rises and the diastolic BP falls after age 60 years in both normotensive and untreated hypertensive subjects [4] and that ISH accounts for 60 to 80 percent of cases of hypertension in older adults [5,6]. Furthermore, the systolic and pulse pressures appear to be the major predictors of coronary disease in older adults; in contrast, diastolic pressure is the major predictor under age 50 years, and all three indices were equal predictors between the ages of 50 and 59 years [7].

## 20.3 Drug Therapy:

Principles of Initiation Therapy:

- Lower initial doses (approximately one-half that in younger patients) should be used to minimize the risk of side effects.
- Older adult patients may have sluggish baroreceptor and sympathetic neural responses, as well as impaired cerebral autoregulation. Thus, in the absence of a hypertensive emergency or urgency, blood pressure should be lowered gradually over a period of weeks to up to six months rather than hours to days in order to minimize the risk of ischemic symptoms, particularly in patients with orthostatic hypotension. This approach is consistent with recommendations made by the European Society of Hypertension/European Society of Cardiology [8].
- Many trials showing benefit from the treatment of hypertension in older adults were performed in relatively fit patients. However, the Systolic Pressure Intervention Trial (SPRINT) included a large number of hypertensive older adults (aged 75 years or older) who were less fit or frail at the time of enrollment. As noted below, the benefits from more intensive blood pressure lowering were present in fit, less fit, and frail older adult patients. Thus, while it is important to be cautious and avoid over-treating frail older adults, this group also appears to benefit from better control of systolic blood pressure.
- When treating older adults and especially frail older adults hypertensive, extra caution is appropriate in the setting of significant orthostatic hypotension.

**20.4 Problem of orthostatic hypotension:** A potential limiting factor to the use of antihypertensive drugs is that orthostatic (postural) and/or postprandial hypotension are found in as many as 20 percent of older adult patients with isolated systolic hypertension [9,10]. Hypertensive older adults with orthostatic hypotension are significantly more likely to fall than those without orthostatic hypotension [11,12]. In addition, antihypertensive treatment in older adult patients is associated with an increased risk of hip fracture during the first one to two months following initiation of therapy [13].

As a result, supine and standing pressures should be measured in older adult patients prior to the initiation of antihypertensive therapy (whether blood pressures are measured in the office or at home). Orthostatic hypotension is diagnosed when, within two minutes of quiet standing, one or more of the following is present:

1. At least a 20 mmHg fall in systolic blood pressure
2. At least a 10 mmHg fall in diastolic blood pressure
3. Symptoms of cerebral hypoperfusion, such as dizziness





Weakness, fatigue, or dizziness following meals may signal postprandial hypotension, which can be verified by timely measurement of BP.

**20.5 Problem of frailty:** With the exception of SPRINT, the randomized trials that showed benefit from the treatment of hypertension in older adults included relatively fit patients since frail patients often have difficulty with participation in such trials. Some observational studies suggest that older adults who are frail may not benefit from antihypertensive therapy. The following studies illustrate a range of findings:

- In a cohort of 1127 frail nursing home residents from France and Italy (aged 80 years and older), two-year mortality rates were highest among those who were treated with two or more antihypertensive drugs and had a systolic pressure less than 130 mmHg (32 percent) [14]. In comparison, mortality was lower among individuals who had higher blood pressure despite taking two or more antihypertensive drugs (20 percent) and among those taking fewer medications, who had systolic BP above and below 130 mmHg (20 and 18 percent, respectively). The adjusted hazard ratio for death was greater for those who had a systolic BP < 130 mmHg while being treated with two or more drugs compared with the other three groups (HR 1.78, 95% CI 1.34-2.37). This association may have been due to a higher prevalence of heart failure and coronary heart disease among those who had lower systolic pressure treated with dual therapy (35 versus 14 percent, and 35 versus 18 percent, respectively).
- In an observational study of 2340 adults older than 65 years, the association between BP and mortality was examined according to whether or not individuals were frail (defined as an inability to walk 6 meters in less than 8 seconds) [15]. Among frail adults, there was no association between BP and mortality. In addition, a higher BP was associated with a lower risk of death among the most frail (ie, those who could not walk the distance at all). The expected association of a higher BP with a greater mortality risk was observed among the fit individuals.

However, the SPRINT trial found a similar benefit from more as compared with less intensive blood pressure lowering in both fit and frail older adults (aged 75 years or older). The prevalence of hypertension among older adults (age greater than 60 to 65 years) is reportedly as high as 70 to more than 80 percent.

1. Older hypertensive patients should attempt lifestyle modification to lower the BP.
2. If goal BP is not attained with lifestyle modification, antihypertensive therapy should be initiated.
3. In the absence of a hypertensive emergency or urgency, BP reduction should always be gradual in older adults. All patients should receive non-pharmacologic therapy, particularly dietary salt restriction (salt restriction should be less stringent in the very old compared to the younger lot) and weight loss in obese patients.
4. Drug therapy should be started if lifestyle changes are not sufficient. Orthostatic (postural) and/or postprandial hypotension should be checked at the initiation.
5. Those who do not have an indication for a specific drug, it is recommended to start with monotherapy with:
  - a. Low-dose thiazide-type diuretic, a long-acting CCB, or an ACE inhibitor/ARB
  - b. In patients with a reasonable likelihood of requiring a second drug (eg, systolic pressure more than 10/5 mmHg above goal), initial therapy with a long-acting dihydropyridine CCB and an ACE inhibitor or an ARB can be added as a combination.



**20.6 Goal BP:** Attain a systolic pressure of 125 to 135 mmHg (office BP) measurements. If goal blood pressure proves difficult then the systolic BP that is reached with two or three antihypertensive agents (even if above target) may be a reasonable interim goal.

**PHL recommends:** The attainment of the tight goal should be left for older patients, who are deemed fit for this. They should be periodically seen in clinic for history with vital check and postural BP assessment. Unless there is a “safety net” of family physician/general practitioner follow-up, this tight control should not be pursued. Home BP check also for those appropriately trained and assessment made according to protocol, as set by the guidelines for home BP monitoring.

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## 21.0 Hypertension in the pediatric population:

Obesity has become an increasingly important medical problem in children and adolescents [1]. Primary hypertension is detectable in children and adolescents and, as in adults, is associated with a positive family history of hypertension, obesity, and life-style factors. Among children and adolescents with primary hypertension; the presence of obesity was associated with marked LVH. Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Renal parenchymal disease is the most common (60 to 70%) cause of hypertension. Adolescents usually have primary or essential hypertension, making up 85 to 95% of cases. The investigations have showed that children in the highest quartile of BP had significantly narrower retinal arterioles than those with lower BP, suggesting that higher BP in childhood is associated with alteration in the microvasculature. There is even emerging evidence that cognitive function is adversely affected by elevated blood pressure in childhood.

In children, the definition of hypertension is based exclusively on frequency-distribution curves for BP [2]. As a consequence, estimates of the prevalence of pediatric hypertension lack a scientific basis. The number of children who might be defined as having hypertension and the frequency with which they develop complications during adulthood remain unknown. However, recent evidence indicates that hypertension in adults originates in childhood, because childhood blood pressure predicts BP in the adult [3,4]. Obese children have approximately a 3-fold higher risk for hypertension than non-obese children [5].

**21.1 Measurement:** BP measurement in the office and ambulatory BP monitoring is recommended [6].

**21.2 Diagnosis:** The diagnosis should be according to the diagnostic protocol and according to the height percentile (see table 13).

- Normal BP: If the systolic and diastolic values are less than the 90th percentile for the child's age, sex, and height.
- Prehypertension: If a child's average BP is above the 90th percentile but below the 95th. Any BP greater than 120/80 mm Hg is also given this diagnosis, even if the BP is below the 90th percentile.
- Stage I hypertension: If a child's BP is greater than the 95th percentile but less than or equal to the 99th percentile plus 5 mm Hg.
- Stage II hypertension: If a child's BP is greater than the 99th percentile plus 5 mm Hg.



Table 13: BP height percentiles in children and adolescents

Ninety-Fifth Blood Pressure Percentiles for 50th and 75th Height Percentiles in Children and Adolescents				
Age (years)	50th height percentile	75th height percentile	50th height percentile	75th height percentile
1	104/58	105/59	103/56	104/58
6	111/74	113/74	114/74	115/75
12	123/80	124/81	123/81	125/82
17	123/80	130/85	136/87	138/87

[Guideline] NHLBI. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004 Aug. 114(2 Suppl 4th Report):555-76.

**21.3 Cuff size:** A pediatric cuff size is to be used for the measurement. For the adolescent the cuff size should be chosen according to the cuff sizes.

#### 21.4 Management of hypertension in the pediatric population:

The PHL endorses the NHLBI guidelines 2011 for management [7]. These guidelines are similar to the ESC guidelines 2009 [8].

- A. **Heart Healthy Lifestyle:** The cardiovascular health integrated lifestyle diet (CHILD 1) diet [9] is specifically designed for cardiovascular disease risk reduction, it can also be used for the promotion of healthy dietary habits for children (older than the age of 2 years) and adolescents while still continuing to provide adequate nutrition for optimal growth and development. The diet provides guidance on caloric distribution, offers appropriate beverage and snack choices, and highlights the importance of adequate fruit and vegetable intake.
- B. **Exercise:** Increases in moderate to vigorous physical activity
- C. **Weight management**
- D. **Drug treatment:** [10]
  1. For children with stage 2 hypertension and stage 1 secondary hypertension or left ventricular hypertrophy, first-line therapy should also include antihypertensive medications
  2. Antihypertensive medication is second-line therapy for children with stage 1 primary hypertension who show no improvement with lifestyle modifications
  3. Insufficient evidence exists to recommend the use of specific antihypertensive agents for specific age groups



4. Losartan, amlodipine, felodipine, fosinopril, lisinopril, metoprolol, and valsartan are tolerated over short periods, and can reduce blood pressure in children from ages 6-17 years but predominantly are effective in adolescents
5. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) should be limited to children aged 6 years or older with creatinine clearance of 30 mL/min/1.73 m<sup>2</sup> or greater
6. Calcium channel blockers are contraindicated in children less than 1 year old
7. Beta-blockers are contraindicated in children with asthma or insulin-dependent diabetes
8. Diuretics are useful as add-on therapy in patients being treated with drugs from other classes; however, potassium-sparing diuretics (spironolactone, triamterene, amiloride) may cause severe hyperkalemia, especially if given with an ACE inhibitor or ARB; all patients treated with diuretics should have electrolyte levels monitored shortly after initiating therapy and periodically thereafter
9. Vasodilators: Tachycardia and fluid retention are common side effects; hydralazine can cause lupus-like syndrome.

It is recommended that once the patient is labeled hypertensive s/he should see a pediatrician for assessment and initial management plan (non-pharmacologic and pharmacologic).

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## 22.0 Secondary Hypertension: [table 14]

This requires a referral to a specialist who deals with hypertension. About 10% of patients with hypertension have a secondary cause. Clinicians often consider secondary causes such as renal disease or coarctation of the aorta in children and young adults aged below 30 years. However, it is important to realize that secondary causes are also common in older patients, particularly primary aldosteronism, renal disease and obstructive sleep apnea (OSA). The prevalence of these conditions is even higher in patients with resistant hypertension [1 - 4]. Other causes, such as pheochromocytoma, are less common but equally important to recognize, as failure to diagnose and treat them can lead to catastrophic consequences [5].

The table gives the signs and symptoms and recommended tests. This condition requires referral to a specialist who deals with the management of secondary hypertension as curing the underlying condition may help cure the hypertension.

Table 14: Causes, signs and symptoms and investigations for secondary hypertension

	Diseases	Signs and symptoms	investigations
1	Renal Artery stenosis	Renal bruit • Worsening in serum creatinine level > 30% after use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	• Ultrasonography (US) of the kidneys (one kidney smaller by > 1.5 cm compared with contralateral) • Duplex Doppler US of renal arteries • Magnetic resonance/computed tomographic renal angiography • Percutaneous renal arteriogram
2	Renal parenchymal disease	Mostly asymptomatic	• Serum creatinine test (elevated level) • Urinalysis
3	Primary aldosteronism	Mostly asymptomatic	• Aldosterone and renin levels (with ratio) • Hypokalaemia (in a minority)
4	Pheochromocytoma	Episodic headaches, sweating, palpitations and flushing • Labile blood pressure (BP)/hypertensive episodes precipitated by drugs: D2-antagonists (e.g. metoclopramide), beta-blockers, sympathomimetics, opioids, tricyclic antidepressants	24-hr urinary fractionated metanephrines
5	Cushing's syndrome	• Moon facies, central obesity, thin skin, easy bruising • Exogenous steroid use	24-hr urinary free cortisol
6	Hypothyroidism/hyperthyroidism	• Symptoms of hypothyroidism or hyperthyroidism (e.g. gain/loss of weight, cold/heat intolerance)	Thyroid function tests
7	Coarctation of the aorta	• Radio-femoral delay • Differential BP in arms and legs (systolic BP > 20 mmHg)	Transthoracic echocardiogram (less accurate in adults)
8	Obstructive sleep apnea	• Obesity • Daytime somnolence, fatigue	Polysomnography
9	Medications	• Oral contraceptives, nonsteroidal anti-inflammatory drugs • Steroids, sympathomimetic drugs (decongestants, diet pills) • Illicit drugs (cocaine, amphetamines, Ecstasy ect.	N.A





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## 23.0 Follow-up: [see table 2]

The patients with hypertension on drug treatment should be followed every 4 – 6 weeks in the beginning while titrating therapy. Thereafter period of follow-up should be 3 – 6 months depending on the local logistics, physician confidence of drug adherence of the patient and control of BP. For the BP range of severe hypertension after appropriate assessment and confirmation the follow-up window could be 1 – 2 weeks. The same follow-up is recommended for patients who are seen with hypertension emergencies and are advised follow-up after the initial treatment settles the BP (for which an initial follow-up of 24 to 72 hours is recommended). For patients with elevated BP (120-129 SBP) the suggested follow-up is 1 year. At which point assessment of healthy lifestyle changes, target weight achievement and exercise routines is made.

## 24.0 Special concerns:

**24.1 Use of sublingual drugs to lower BP acutely:** It has been a practice that has been highlighted in surveys and studies that sublingual drugs like nifedipine and captopril are used to bring down severely elevated BP. It has been stressed in the section of HTN crises that for both severe HTN (BP >180/120 mmHg) and no symptoms with or without chronic target organ damage the use of sublingual drugs is contraindicated. Although used in the past, sublingual or oral nifedipine is no longer recommended due to its propensity to cause severe hypotension and organ ischemia. [1] A lot of short acting drugs have been used in the past to bring down severely elevated BP but are discourage now as a sharp decrease in BP may lead to loss of consciousness, ischemic stroke, and myocardial infarction [2].

## 24.2 Use of anxiolytics as first line antihypertensive therapy:

The use of anxiolytics in hypertension has been in vogue and is not based on robust scientific evidence. It has been noted in studies that benzodiazepines can lower BP in patients, who have objective evidence of anxiety as demonstrated by visual anxiety scales [3, 4].



The use of benzodiazepines for chronic treatment of arterial hypertension is far to be advisable at all ages [5]. It has been seen, in a study of clinical practice patterns of benzodiazepine use, that 21% of patients took benzodiazepines for hypertension treatment [6]. The use of benzodiazepines in Pakistan (largely because of over the counter availability) is noted to be higher than other developing countries and only a small fraction see a psychiatrist for the same [7].

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### 25.0 Summary/Conclusion:

Hypertension emerges as one of the most important global health issues. We have enough data to form a strategy to address the problem in a cost effective manner, both at the individual level as well as the population level. The strategy addresses BPs considered normal in the past. We know that SBP above 115 mmHg carries a risk. We also now know that tight control of BP to around or less than SBP 120 carries benefit with acceptable level of adverse effect. It is also known that the non-pharmacologic strategy have benefits and this is a strong recommendation. Therefore, the PHL guidelines now define the non-pharmacologic approaches in steps 0, 1 and 2. The step 0 is awareness and education to a population, who do not yet have high BP. This is in keeping with the home health education that was given in the COBRA trial and yielded significant benefit This will help us create an awareness level using step 0 as a tool rather than just an idea. Step 1 then becomes a recommendation with a plan. However, it has been noted that of the strategies non-pharmacologic approaches are adhered to and followed up in the least strict manner. The step 1 is therefore defined as a recommendation for home. Step 2 then becomes a supervised program for exercise, diet and smoking cessation.



Drug therapy includes the ACD as first three drugs and spironolactone as the 4th line therapy. Additionally, doxazosin and bisoprolol are the 5th and 6th line therapy. ACE inhibitors are to be considered the first line for most patients with ARBs to be used as alternate options. For diuretic the longer ones are preferred over HCTZ that is chlorthalidone and indapamide.

Special populations are defined, HTN in pregnancy, the elderly and in the pediatric population. Similarly, HTN crises are defined and clear distinctions are made between severe HTN, HTN urgencies and emergencies. In the end the problem of anxiolytics being used as first line anti HTN therapy, use of sublingual drugs (other than angised for angina) for lowering severe HTN are clearly discussed and discouraged.

The guidelines carry at the end, case vignettes that have been provided so that the users can become familiar with the document by using them. This will keep the document as an active clinical tool.



## 26.0 Case Vignettes

**Calculators: The smart BMI:** : <https://www.smartbmicalculator.com/?ru=0tools.acc.org/ASCVD-risk-estimator-plus/#!/calculate/estimate/>.

### Case 1:

A 55 years old man comes to your clinic. He has been noted to have borderline high BP on multiple occasions checked at a friend's house. He wants to check his BP at home as he has read on the Internet that home BP self-monitoring gives a better reflection of the true BP status. He went to the medical surgical store and was confused to see the various apparatuses. He has liked a very portable aneroid BP apparatus, as he is uncomfortable with the mercury one. He has also heard that the digital devices are unreliable.

Q1: Which apparatus is considered the gold standard for BP measurement?

Q2: Should he buy the aneroid BP apparatus?

Q3: Is his concern about the digital device valid?

Q4: What should he ensure before buying any device?

Q5: What is calibration?

(See section 4.0 and 6.4, page no 6 and 12)

### Case 2:

A 43 years old Bank executive visits you. She has been noted to have high normal BP. She has a stressful life and does not sleep well, for which she takes benzodiazepines. She has a step count application on her mobile phone and does about 3000 steps in 24 hours. She likes to take "sheesha" every time she eats out, which is often. She has family history of hypertension from both sides. She is 156 cm tall, weighs 72 kg. Her BP in the clinic is 138/88 mmHg and 135/85 taken 5 minutes apart in the right arm. Her waist is 115 cm. Rest of the exam is unremarkable. There is no difference in the two arms. Her lipid profile is LDL: 143 mg/dL, HDL: 32 mg/dL, TGs: 192 mg/dL; Fasting sugar 113 mg/dL. Urine detailed report is normal. Her ECG is within normal limits.

Q1: What are the risk factors that can be identified here?

Q2: Is she sedentary?

Q3: Is "sheesha" safe?

Q4: Is there an invisible risk factor here?

Q5: How do you see her lipid profile?

(See section 12.0 to 15.0, page no 25 and 28 )

### Case 3:

A 49 years old lawyer visits you for high BP. He smokes and has family history of premature coronary artery disease. He is active and walks for 30 minutes daily. His pulse is 87 bpm, BP: 150/90 mmHg, rest of the exam is unremarkable. Weight: 89 kg, Height: 167 cm. His lipid profile is Total cholesterol: LDL: 179 mg/dL, HDL: 30 mg/dL, TGs: 170 mg/dL; Fasting sugar 108 mg/dL. Urine detailed report is normal. ECG is within normal limits.



Q1: What is his BMI?

Q2: Calculate his 10-year risk of CV event.

Q3: What is the role of low dose Aspirin for primary prevention of CV event?

Q4: What is the role of statins for primary prevention of CV event?

(See section 12.0 to 14.0, page no 25 and 28)

#### Case 4:

A 39 years old doctor is in your follow-up. His BP office BP is 145/90 mmHg; home BP monitoring: 140/85mmHg (average of 28 readings over 7 days); ABP over all mean 135/80 with loss of nocturnal dip in BP and no white coat effect. He used to smoke till a month ago. He walks for 20 minutes daily. His pulse is 78 bpm, rest of the exam is unremarkable. Weight: 89 kg, Height: 173 cm. His lipid profile is Total cholesterol: LDL: 150 mg/dL, HDL: 36 mg/dL, TGs: 150 mg/dL; Fasting sugar 104 mg/dL. Urine detailed report is normal. ECG is within normal limits.

Q1: What will be the plan for a non-pharmacologic approach?

Q2: Would you like to suggest a change to his exercise routine?

Q3: He wants to know about isotonic exercise to control BP.

Q4: Is there a role of programmed exercise training under supervision as part of BP control?

(See section 15 with Tables 6 and 7, page no 28, 29 and 31)

#### Case 5:

A 43 years old school teacher has been noted to have high BP on multiple occasions checked randomly. She states that she has been under stress due to added responsibilities at work. Her pulse is 78 bpm, BP 145/80 mmHg; rest of the exam is unremarkable. Weight: 65 kg, Height: 165 cm. Her lipid profile is Total cholesterol: LDL: 112 mg/dL, HDL: 45 mg/dL, TGs: 135 mg/dL; Fasting sugar 94 mg/dL. Urine detailed report is normal. ECG is within normal limits.

Q1: She wanted to know if she is hypertensive.

Q2: How would you like to assess her further and what do you want ruled out?

Q3: What would you be your treatment target?

Q4: What is the role of benzodiazepines as 1st line treatment in her case?

Q5: What is the BMI?

(See section 11 with Table 5 and Figure 2; Section 15.1; Section 24.2, page no 21, 22, 24, 28 and 57)

#### Case 6:

A 76 years old businessman has been diagnosed with hypertension. His pulse is 79 bpm, BP160/60 mmHg, while the rest of the exam is unremarkable. Weight: 64 kg, Height: 175 cm. The lipid profile is Total cholesterol: LDL: 96 mg/dL, HDL: 39 mg/dL, TGs: 112 mg/dL Fasting sugar 94 mg/dL. Urine detailed report is normal. ECG shows LVH by voltage criteria.

Q1: What is BP pattern showing and what is concerning about that?

Q2: He wants to know what happens to the BP in old age.

Q3: How will you initiate drug therapy in this case?

Q4: Which hemodynamic parameter should you be checking in the clinic on follow-up?

(See section 20, page no 49)



**Case 7:**

A 47 years old state agent comes to you for assessment. He does not have any known cardiac risk factors. There is family history of hypertension. He smokes and has a sedentary lifestyle. He takes 6 – 12 cups of tea with sugar a day. On examination his funduscopy shows changes in the retina that are suggestive of HTN. The ECG reveals LVH by voltage criteria. The BP noted in the clinic on multiple occasions is <140/90 mmHg.

Q1: How will you explain these HTN changes by the normal clinic BPs?

Q2: What are the modalities that can help you investigate the BP further?

Q3: What is the percentage of this phenomenon seen in clinical practice?

Q4: Would you commence treatment for HTN?

(See section 17.2 and Section 11, page no 40, and 21)

**Case 8:**

A 34 years old woman comes to you in her 28th week of gestation. She has family history of hypertension but she has always had normal BP values. She has been active in life and careful with her diet. Her BP is 150/80 mmHg (average of two readings taken 4 hours apart in the clinic). Rest of her physical exam is unremarkable. Her ultrasound reveals the baby is thriving and normal for gestational age.

Q1: Is she hypertensive? And if yes what kind of hypertension are we seeing?

Q2: What will be your next step?

Q3: Will you start drug treatment and if yes then which drug?

Q4: How long will you continue surveillance of BP for after the gestation?

(See section 19, page no 44)

**Case 9:**

A 66 years old lawyer has come to you with uncontrolled very high BPs but no symptoms. He has history of old limited anterior wall MI, for which a primary angioplasty was done. His echocardiogram shows LVEF of 50-55%. He is on ASA 75mg1, Clopidogrel 75mg1, bisoprolol 5 mg1, felodipine 7.5 mg1. The pulse is 79 bpm, BP190/125 mmHg, while the rest of the exam is unremarkable. Weight: 87 kg, Height: 172 cm, BMI 29. The lipid profile is Total cholesterol: LDL: 96 mg/dL, HDL: 37 mg/dL, TGs: 149 mg/dL. Fasting sugar 101 mg/dL. Urine detailed report is normal. ECG shows Q in lead III only.

Q1: What is this condition?

Q2: He is worried that he is going to have another heart attack and wants sublingual nifedipine as taken previously. Do you agree with his request?

Q3: What will be your plan for treating the BP?

Q4: How would your management differ if he now started to have chest pain?

(See section 18 and Table 5, page no 41 and 22)

**Case 10:**

A 45 years old civil servant has come to you with diagnosed hypertension with a 6 months follow-up after a good run of non-pharmacologic intervention. The pulse is 72 bpm, BP160/90 mmHg, while the rest of the exam is unremarkable. Weight: 74 kg, Height: 165 cm (BMI 27). The lipid profile is Total cholesterol: LDL: 140 mg/dL, HDL: 34 mg/dL, TGs: 139 mg/dL. The fasting sugar is 113 mg/dL. Urine detailed report shows 1+ proteins. ECG shows LVH.





Q1: How would you initiate drug therapy? What is the drug of choice?

Q2: Which drugs would you avoid in combination for this patient?

Q3: How would you ensure drug compliance?

(See section 16 and Table 9a, 9b and Figure 3, page no 34 and 35)

#### Case 11:

A 45 years old civil servant has come to you with diagnosed hypertension with a 6 months follow-up after a good run of non-pharmacologic intervention. The pulse is 72 bpm, BP160/90 mmHg, while the rest of the exam is unremarkable. Weight: 74 kg, Height: 165 cm (BMI 27). The lipid profile is Total cholesterol: LDL: 140 mg/dL, HDL: 34 mg/dL, TGs: 139 mg/dL. The fasting sugar is 113 mg/dL. Urine detailed report shows 1+ proteins. ECG shows LVH. He was started on an ACE inhibitor and diuretic and now is following up after 6 weeks. The BP now is 125/80 mmHg. He is complaining of irritation in the throat and hacking cough and his labs show sodium 120, potassium 3.8

Q1: How will you manage the cough?

Q2: Was starting two drugs in this case appropriate?

Q3: What would be an ideal combination in this case?

(See section 16 and Table 9a, 9b and Figure 3, page no 34 and 35)

#### Case 12:

A 63 years old colonel has been following you for HTN. His BP's were very well controlled. He was on Indapamide SR 1.5 mg1. He is very active and plays golf and very particular about his diet. His BMI is 23 with a waist of 88 cm. His BP in the recent visits has gone up to 170/90 mmHg despite adding a full dose ARB and CCB. His labs reveal sodium 140, potassium 4.5, BUN 35, creatinine 1.9 mg/dL; TG 123 mg/dL, LDL 70 mg/dL, HDL 50 mg/dL.

Q1: What is the likely diagnosis?

Q2: How will you investigate the patient?

Q3: What would be the likely cause had this been a 35 year old woman?

Q4: What can be done more to treat this condition?

(See section 22, page no 56)

#### Case 13:

A 57-year old headmistress has been following you for HTN. Her therapy has been titrated over a period of 6 months to maximum doses of an ACE inhibitor, CCB and HCTZ. She leads a sedentary life due to work and osteoarthritis. Her BMI is 32 with a waist of 120 cm. The BP in the recent visits has gone up to 150/90 mmHg. The labs reveal sodium 137, potassium 4.2, BUN 24, creatinine 1.0 mg/dL; TG 176 mg/dL, LDL 150 mg/dL, HDL 32 mg/dL; FBS 120 mg/dL and HbA1c 6.3%.



Q1: What would be the fourth line therapy?

Q2: She being a teacher, wants to know what would be the evidence-based choices after the 4th line failed?

Q3: What is the common side effect of the 4th line therapy?

Q4: What other non-pharmacologic intervention would you reiterate upon and how?

(See section 16 and Figure 3, page no 34 and 37)

**Case 14:**

A 66-year old retired professor comes to you for treatment of hypertension. He has been diagnosed with HTN by having an Ambulatory BP, which showed an overall daytime mean BP of 150/90 mmHg. He has dyslipidemia and is on statin therapy. He is otherwise active and is particular about his diet and maintains his weight close to his healthy weight.

Q1: According to current data what should be his BP treatment target?

- A. <130/90 mmHg
- B. <120/80 mmHg
- C. <130/80 mmHg
- D. <140/90 mmHg

Q2: The professor wants to know how many drugs would he would be expected to take to achieve the target?

Q3: To achieve this target how would you like to check his BP on follow-up visits?

- A. Home BP monitoring
- B. Ambulatory BP
- C. Repeated BP measurements in the clinic with mercury apparatus
- D. Use repeated oscillometric (digital) BP measurement

(See section 6.5, 11, 16, page no 12, 21 and 34)

**Case 15:**

A 34-year old woman presents is diagnosed with hypertension. She is obese with a BMI of 30 and waist circumference 112 cm. BP 150/90 mmHg, pulse 74 bpm. Rest of the exam is unremarkable. ECG is with in normal limits. The urine DR is normal. TG 164, HDL 27, LDL 149 mg/dL; FBS 122 and HbA1c 6.1%.

Q1: What is her 10-year CVD risk?

Q2: What is the drug of choice?

Q3: Which drug would you avoid and why?

Q4: In terms of non-pharmacologic intervention, which diet would you recommend for her?

(See section 12, 15.4, 15.5, 15.7, Table 8 and Section 16, page no 25, 28, 33 and 34)

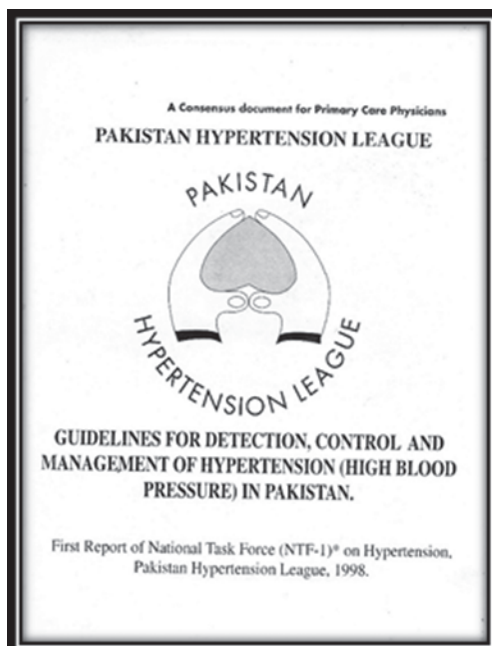


# Pakistan Hypertension League Glimpses

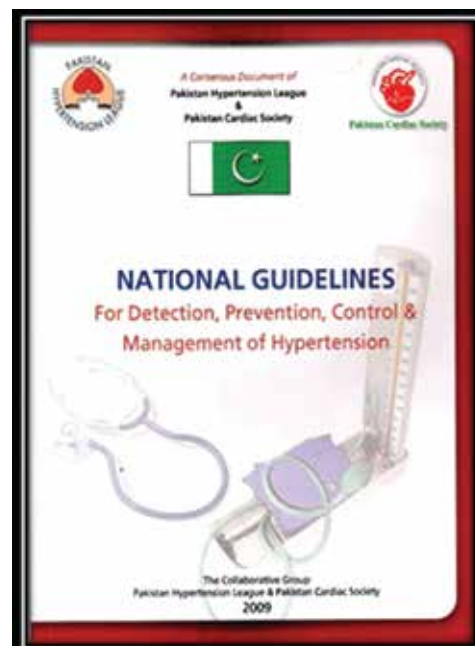


PHL Founded on June 1997  
Prof. Azhar M Farooqi & Prof. Mohammad Ishaq

## 1<sup>st</sup> Guideline



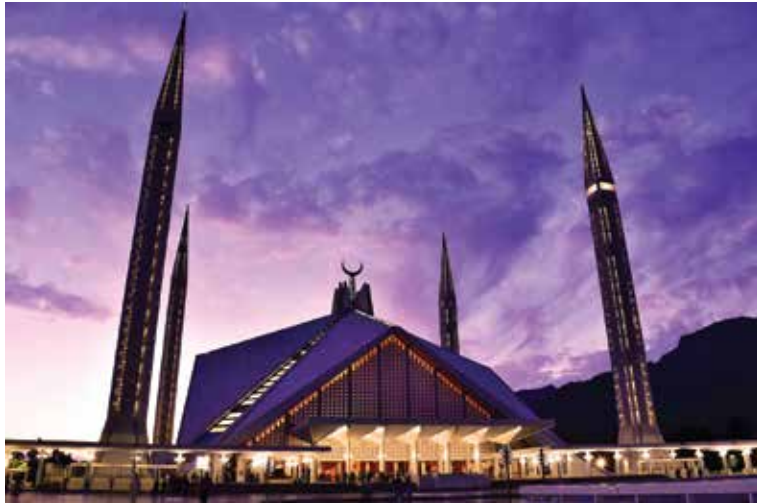
## 2<sup>nd</sup> Guideline



# First Guideline Preparation by PHL Team







## ISLAMABAD: Shah Faisal Mosque

Faisal Mosque is the mosque in Islamabad, Pakistan. Located on the foothills of Margalla Hills in Islamabad, the mosque features a contemporary design consisting of eight sides of concrete shell and is inspired by a Bedouin tent. The mosque is a major tourist attraction, and is referred to as a contemporary and influential feature of Islamic architecture.



## BALUCHISTAN: Ziarat

Ziarat the capital of Ziarat District, Balochistan Province, Pakistan. It is a holiday resort, about 130 km from the capital city of Balochistan province Quetta. The famous Quaid-e-Azam Residency is also there in the valley, where Quaid spent a few of his most memorable days.



## FATA: Shagai Fort

Shagai Fort is a fort located 13 kilometres from Jamrud in Khyber Agency, Federally Administered Tribal Areas. It was built in 1927 by the British forces to oversee the Khyber Pass. Now it's manned by Pakistani military and paramilitary troops.

## GILGIT - BALTISTAN: KHUNJERAB PASS

Khunjerab Pass or (elevation 4,693 metres or 15,397 feet) is a high mountain pass in the Karakoram Mountains in a strategic position on the northern border of the Pakistani region of Gilgit–Baltistan Hunza – Nagar District on the southwest border of the Xinjiang region of China. Its name is derived from two words of the local Wakhi language : 'Khun' means Blood and 'Jerav' means a creek coming from spring water/water falling.





### KHYBER PAKHTUN KHUWAH: Khyber Pass

The Khyber Pass: 1,070 m or 3,510 ft) is a mountain pass connecting the Pakistani town of Landi Kotal, near the Afghanistan border, to the Valley of Peshawar at Jamrud by traversing part of the Spin Ghar mountains. An integral part of the ancient Silk Road, it has long had substantial cultural, economic, and geopolitical significance for Eurasian trade.

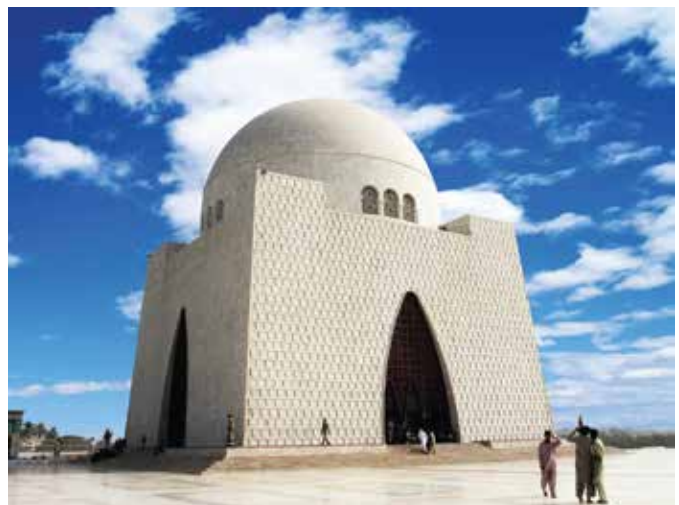


### PUNJAB: Minar-e-Pakistan

Minar-e-Pakistan is a public monument located in, adjacent to the Walled City of Lahore, in the Pakistani province of Punjab .[1] The tower was constructed during the 1960s site where the All-India Muslim League passed the Lahore Resolution on 23 March 1940 - the first official call for a separate and independent homeland for the Muslims of British India, as espoused by the two-nation theory.

### SINDH: Mazar-e-Quaid

Mazar-e-Quaid (Urdu: مزار قائد), also known as the Jinnah Mausoleum or the National Mausoleum, is the final resting place of Quaid-e-Azam ("Great Leader") Muhammad Ali Jinnah, the founder of Pakistan. Designed in a 1960s modernist style, the mausoleum also contains the tomb of his sister, Māder-e Millat ("Mother of the Nation") Fatima Jinnah, and that of Liaquat Ali Khan, the first Prime Minister of Pakistan. The mausoleum was completed in 1970, and is an iconic symbol of Karachi. The mausoleum is one of the most popular tourist destinations in Karachi.





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