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4th National Hypertension Guidelines

FOR THE PREVENTION, DETECTION, EVALUATION AND MANAGEMENT OF HYPERTENSION

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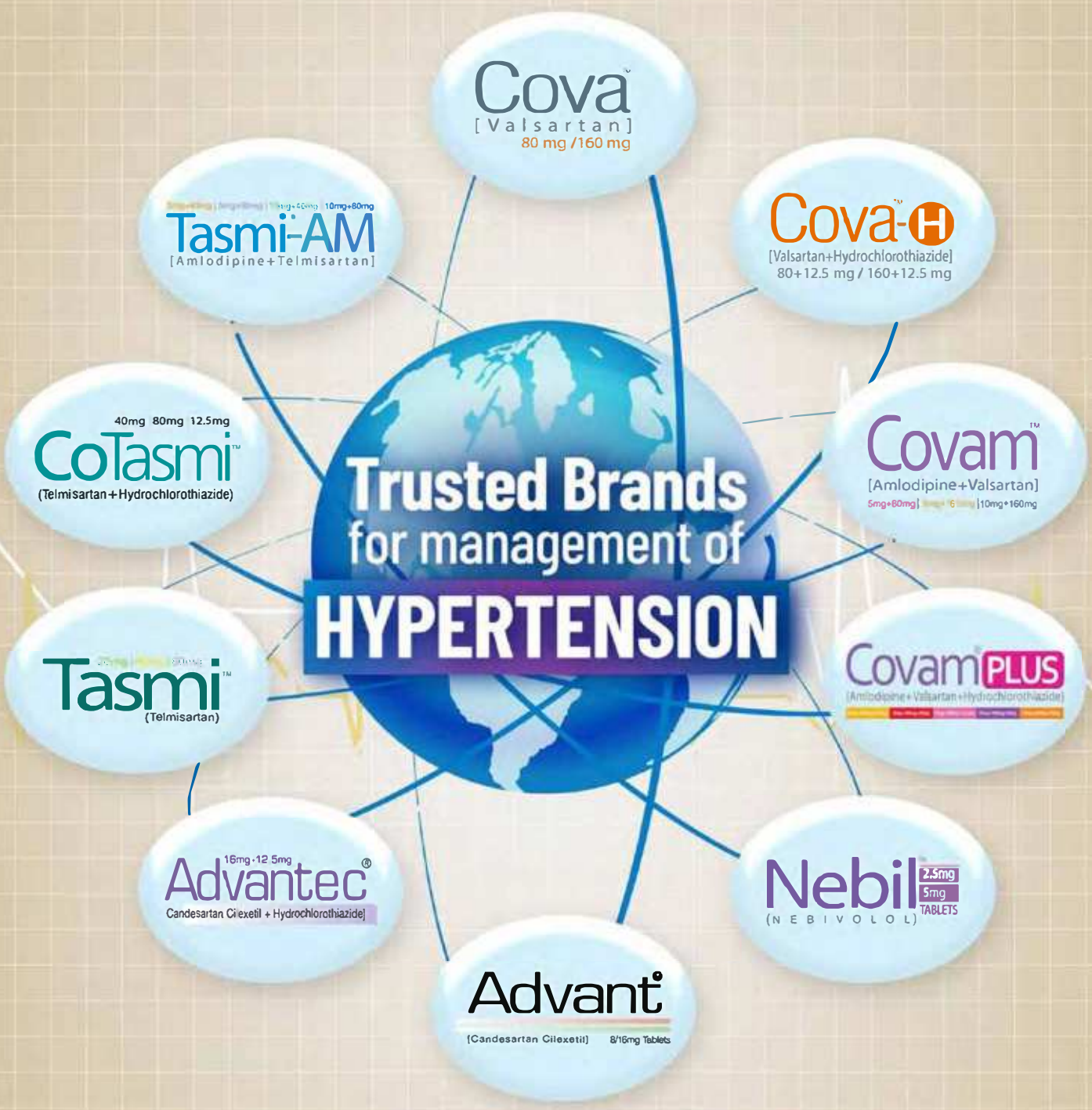

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ENDORSEMENT MESSAGE BY PAKISTAN CARDIAC SOCIETY

Hypertension remains a world-wide public-health challenge and is a leading cause of stroke, heart disease, and the progression of chronic kidney disease. Despite advances in our understanding of its development and treatment, hypertension is on the rise and is projected to afflict over 50% of adults worldwide by 2025. Given the fact that this disease is a "silent killer," a better understanding of its pathogenesis through research and identifying more optimal ways to prevent and detect it, may have a significant impact on the quality of care..

The Pakistan Cardiac Society is pleased to endorse the National Hypertension Guidelines (NHG), which is the fourth update of the first document prepared in 1998. The PHL, in collaboration with Getz Pharma, has taken a great initiative in publishing these national guidelines as a JPMA supplement, which is a prestigious peer-reviewed, indexed medical journal from Pakistan.

The JPMA supplement is solely intended to help doctors make standard clinical decisions regarding the diagnosis, treatment, management, and control of hypertension. The guidelines will contribute to enhancing medical knowledge regarding hypertension and its associated diseases, and they should be utilized with the approach of continuing research for new insights and suggestions. This is just one step in the lengthy journey of enhancing healthcare, and the only way to ensure the effectiveness of guidelines is to implement them in the clinical setting for standard of care practices.

Prof. Jawaid Akbar Sial
President, Pakistan Cardiac Society
Executive Director, Sindh Institute of Cardiovascular Diseases

ENDORSEMENT MESSAGE BY PAKISTAN HYPERTENSION LEAGUE

The field of hypertension is a dynamic subject with new evidence and questions emerging; therefore, the guidelines are always under constant review. I am glad that PHL was able to launch the 4th version of national hypertension guidelines at the Pakistan Hypertension League (PHL) 25th annual conference in 2022.

On behalf of PHL, I am pleased to endorse the National Hypertension Guidelines and their supplement publication in the internationally recognized medical journal JPMA. Hypertension is one of the most preventable causes of premature morbidity and mortality worldwide, and Pakistan is no exception. We need to create awareness regarding the management, treatment, and control of hypertension, and the best way to do it is through local guidelines. I would like to acknowledge the efforts of the chairman of the writing committee, Prof. Dr. Aamir Hameed Khan, and the Public Health Department, Getz Pharma, for the publication of the "JPMA Supplement on National Hypertension Guidelines". As knowledge about hypertension has exploded exponentially, what is now needed is to convert that knowledge into clinical practice.

I urge our cardiac fraternity, physicians, and general practitioners to make great use of this national document for standard of care practices. I am sure this dedicated work will be a great source of reference for our medical community.

Prof. Feroz Memon
President, Pakistan Hypertension League
Vice Chancellor and Principal, Indus Medical College Hospital

CONTENTS

PAGES

CONTENTS

PAGES

CONTENTS

PAGES

CONTENTS

PAGES

EDITORIAL

Hypertension in Pakistan: Way Forward for A Not So Silent Epidemic

Adnan Ahmad Khan,[1,2] Taimoor Ahmed,[2] Aisha Tauqeer[3]

Hypertension is a leading cause of morbidity and mortality globally through its effects on chronic diseases such as cardiovascular diseases, stroke, and heart attacks. The World Health Organization estimates that 1.4 billion people live with hypertension and this number will increase to 1.56 billion by 2025.[1] Hypertension is estimated to cause 7.5 million or 13% of all deaths in world or around 57 million disability adjusted life years.[2]

In Pakistan around 18% of all adults and 33% of those over 45 years of age have hypertension, however, only around half of all such individuals receive any treatment.[3] Multiple factors that lead to insufficient treatment of hypertension include supply side factors such as a lack of trained healthcare providers and access to adequate medicines, as well as a lack of demand or understanding of the disease by the patients.

In Pakistan there is a large network of more than 15,000 government facilities and nearly 200,000 private providers, including doctors and others, that serve communities with medical care.[4] If a significant number of these providers were able to effectively diagnose and manage hypertension, it would greatly contribute to addressing this condition. However, numerous studies have shown that few of these providers have sufficient knowledge of hypertension. In this regard, development of the comprehensive 4th National Hypertension Guidelines is a key step. It would help standardize diagnosis and treatment of hypertension and allow standardized training of providers at a national scale. The recently launched Prevention, Management and Control of Hypertension (PREACH) project seeks to build on precisely this concept by training 5,000 general practitioners across Pakistan in diagnosis and treatment of hypertension.

The importance of such training cannot be emphasized enough. Most providers, and their patients, are accustomed to managing acute ailments or injuries, where the condition is "cured", and there is little need for follow-up care. However, the management of hypertension represents a paradigm shift towards long-term disease management rather than a cure. The treatment is usually lifelong and requires a resetting of "normal" as a life with lifestyle changes and blood pressure medicines. This often goes against the traditional notions in society where a person is the healthiest in their natural state without medicines. Thus, many would wait to treat complications of hypertension such as strokes, heart attacks or renal damage, without understanding that regular and effective management of hypertension through medicines and lifestyles could have prevented these and saved considerable misery and costs. Thus patients, and sometimes the providers, need to be convinced of the new norm where the natural state is a normal blood pressure albeit with medicines and lifestyle modification.

Even when this paradigm is internalized, it is difficult to keep taking medicines diligently and to see a doctor as a "well visit". Considerable global literature suggests poor compliance to medicines and lower still for lifestyle changes.[5] This adherence is further limited by the fact that most providers are constrained for time and don't spend the 20-30 minutes for counselling during their visits. Providers must be trained in counselling to achieve these goals, and to address queries or concerns and to reinforce the need for compliance with the medicines and lifestyle changes. To change from this to devoting sufficient time for counselling is a paradigm shift for providers who may see this as imposition on their "productive time". A public health approach is needed that would illustrate to providers that by spending more time with each patient they would expand their clientele by introducing a new category of patients that requires repeated wellness checks for a chronic condition, that would otherwise be missed or only seen in case of a complication.

However, availability of treatment in communities is one step, albeit an important one, in hypertension management. Even when they have access to the best care possible, nearly half of patients will discontinue their therapy within twelve months.[6] More importantly, in a system that relies on healthcare providers to make the

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first diagnosis, will necessarily miss many patients while they are well and only identify them after they have had complications.

This suggests that an option may be to bring diagnosis and possibly some treatment to the patient's doorstep. Considerable experience from immunization, family planning and COVID-19 vaccination in Pakistan and of managing hypertension elsewhere suggests that while many individuals may recognize the need for such services, they will not actively seek them out.[7,8] Many factors underlie this reluctance, including opportunity costs for those who spend much of their time making ends meet, limited access to health facilities and potentially costs. Experience also shows that these may be overcome through community outreach. This was successfully demonstrated for maternal and child health through the lady health worker programme and then has subsequently been replicated even more successfully in the private sector.[9]

Outreach can be used both to identify new diagnoses, to counsel in lifestyle changes, provide wellness check through home blood pressure monitoring, even to teach home self-monitoring and referrals to providers when changes or higher-level services are needed.[10] This would establish a network of outreach workers that are linked with local providers. There is some evidence from family planning that in some of these cases, the costs of outreach may be assumed by the local providers who see them as a source of additional revenue.[11]

Finally, there is a need to better understand hypertension and its management in the Pakistani context. There is a need to define what has worked and what has not, to understand patient attitude towards the condition, towards taking medicines chronically and the trade offs that they sometimes must make and more. This would require cross section of not just conventional medical research but also elements of social sciences, behavioural economics and most importantly, the use of community trials to understand what works. Perhaps over time a national hypertension research agenda can be developed to specify priorities in hypertension management as seen through an experiential approach by experts and practitioners.

This is by no means an exhaustive list of asks for a silent epidemic that is insidiously contributing high burden of disease and premature deaths, but can be managed through available and accessible means. As our experience with managing hypertension grows, so will our understanding and its sophistication, and this will surely enhance patient care and the overall impact of hypertension and perhaps even other non-communicable diseases in Pakistan.

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PREACH Implementation Project
A Socio-Ecological framework for Hypertension in Pakistan

Wajiha Javed, Jaffer Bin Baqar, Samra Maqbool

Background

The latest estimate suggest that 1.4 billion people are living with hypertension globally1 and World Health Organization (WHO) predicts hypertension shall affect 1.6 billion people across the world by 2025, approx. 29% of world's population.2 Moreover, worldwide, hypertension is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS.3

It is alarming that, fifty-four percent of strokes and forty-seven percent of cardiovascular deaths are caused by suboptimal control of blood pressure.4 By the time hypertension is diagnosed in a patient at a tertiary care hospital, one organ is already damaged. According to the National Health Survey (2010), 33% of adults aged 45 years and 18% of all adults in Pakistan were hypertensive, and every third hypertensive aged 40 years and above was susceptible to an extensive range of diseases. This survey also revealed that only half of the diagnosed hypertensive subjects were treated at any time, making the prevalence of controlled hypertension only 12.5%.5 Hypertension knowledge in hypertensive patients is not adequate and is alarmingly poor in patients with uncontrolled hypertension.6

One of the reasons of unsatisfactory clinical management of the disease is a lack of standardized approach across Pakistan. A National Standardized Guideline is needed for the Public Sector (30% of Patients)7 to address the issue of varying clinical practices. A developing country does not have resources to manage complications of hypertension as stroke, Myocardial Infarction, Heart Failure, etc. Therefore, early surveillance and community screening is the ONLY means to detect early onset of hypertension. (Possibly 10 – 15 years can be added before organ damage is revealed). A more cost-effective strategy probably for the country is to reduce the burden on tertiary care hospitals and to make GPs as first line respondents. BP control can only be achieved if those individuals with hypertension are identified, diagnosed, and treated timely at the community level.

The alarming situation of deteriorating state of Pakistan's economic and health infrastructure demands concrete measures to be taken. Therefore, Getz Pharma takes pride in launching a project called PREACH 'Prevention, Management and Control of Hypertension' aiming to ignite a paradigm shift from tertiary hospitals to primary care facilities and from treatment alone to preventive care. Additionally raising awareness in the general masses and developing a trained force to battle against this silent killer – hypertension.

Goal

Reducing the burden of hypertension from tertiary care to primary care and from specialist to general practice.

Objective

The primary objectives of PREACH are the following:

1. Train the registered healthcare practitioners on standard national guidelines through the train the trainer model
2. Educate & Create Awareness in the individual and community at large on home blood pressure monitoring
3. Mapping and advising for self-referral pathway
4. Forming a National Hypertension Registry
5. Establishing an enabling environment for inclusion of hypertension in the essential primary package.

PREACH Implementation Plan – Multi-sectorial Strategy (Figure 1) Supply

1. A standardized curriculum and assessment forms will be prepared derived from the updated national hypertension guidelines.
2. A capacity building training of registered doctors (senior & young consultants, family physicians, and general practitioners) across Pakistan on the standard curriculum.
3. Simultaneously impact assessment studies will be carried out to evaluate the effectiveness of the PREACH project.

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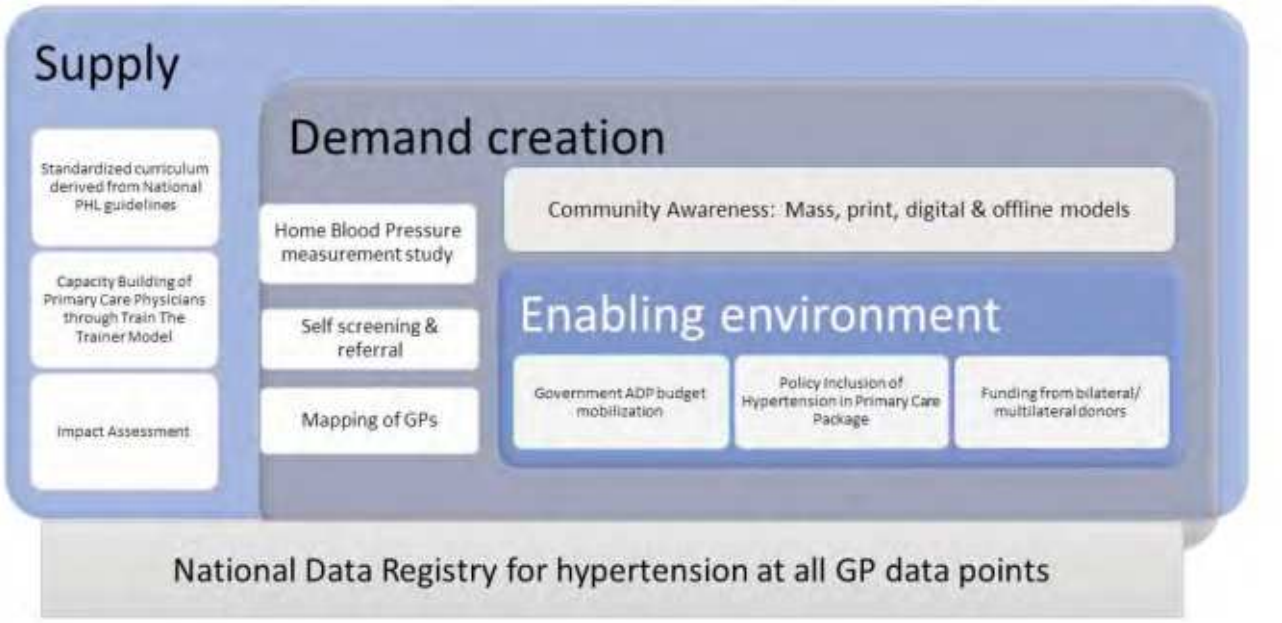

Figure-1: Implementation Model of Project PREACH.

Demand creation & Community Awareness

4. A scientific study will be conducted with academic partners to identify and create easiest methods for diagnosis of hypertension through home blood pressure monitoring.
5. A standard mass grassroots level awareness drive will be developed to create awareness in individuals and community on hypertension screening and home blood pressure monitoring.
6. Self-screening and self-referral pathway and mapping of GP's for timely diagnosis and management of hypertension.

Enabling environment

7. Discuss with Government officials to include project PREACH in annual development programmes and for budget mobilization.
8. Doing advocacy for policy inclusion of hypertension in primary care package.
9. Generating funds from local and international bilateral/multilateral donors.

National Hypertension Registry

10. Development of a national hypertension registry for robust data collection, analytics, and evidence based publications for informed clinical decisions.

The Socio-Ecological model of project PREACH – A framework for the prevention of

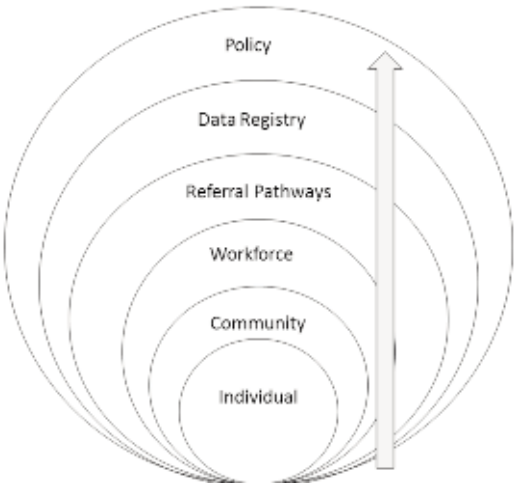

Figure-2: 6 step Socio-Ecological model adapted for project PREACH
Note: The socio-ecological model is excerpted from cdc.gov and modified for the PREACH project.

Hypertension in Pakistan (Figure 2)

The PREACH project is designed with an approach to bring a change on population level with integration of all societal level determinants that influence hypertension for e.g. physician-patient gap in healthcare service delivery, lack of early screening and diagnosis of hypertension on primary level.

Therefore, the first pivot is bringing change on individual level by encouraging people to self-screen themselves at home and self-refer themselves to trained practitioners. Simultaneously, the general practitioner workforce will be

trained to standardize the health services (hypertension treatment) in the community. The idea is to create demand from the community through self-referral to GP and from there to tertiary care level and supply it by building the capacity of health practitioners via train the trainer model which includes cascade down training sessions resulting in a workforce ready to defeat hypertension.

After achieving this milestone, the project's objective is to build a 1st national data registry on hypertension resulting in building a database of patients which will enable the policy maker to devise particular action plans and targets for the prevention of hypertension disease in Pakistan. Furthermore, building strong liaison with policy advisors to advocate on bringing hypertension to essential healthcare package of Government of Pakistan for NCD's.

With this framework, the aim is to synergize multiple sectors to come forward and work towards one approach i.e. to reduce the hypertension burden in Pakistan.

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NATIONAL HYPERTENSION GUIDELINES

FOR THE PREVENTION, DETECTION, EVALUATION AND MANAGEMENT OF HYPERTENSION

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 (hypertension mediated end organ damage).[1]

1.1 Global Perspective

Around 31% of the global population i.e. 1.4 billion people worldwide have been diagnosed to have hypertension; though 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 imposed on the lower and middle income countries.[2] The mean BP levels have particularly increased over the years in South and Southeast Asia, East and West Africa and Oceania.[2-4] Suboptimal blood pressure costs about 10% of the world's total healthcare budget, and if the current scenario remains, uncontrolled BP 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 Pakistan Perspective

The National Health Survey of Pakistan based on 1990 to 1994 reported that 19% of people in the country had hypertension, with every third person over the age of 45 years being hypertensive.[6] More recent data suggests that the overall prevalence of hypertension has increased and ranges between 34% in one study[7] to 37.3% in another.[8] Awareness rate of this chronic disease has steadily increased from 15% in men and 36% in women[6] in 1990-1994, to up to 42% in 2002[9] and 62% in 2017.[7] The major concern is that only half of the people with hypertension are diagnosed and only 50% of the ones diagnosed are actually treated for it.[10, 11] Amongst the hypertensive population, the rate of control is very poor. More than 70% of hypertensive patients have uncontrolled blood pressures.[12] Amongst the three South Asian countries including Pakistan, Sri Lanka and Bangladesh, Pakistanis have the poorest rate of blood pressure control.[12] Amongst children between the ages of 5 to 17 years, the prevalence of hypertension is 3.4%.[6] As age of the population 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.[6,12] Amongst both genders, more women suffer from hypertension in Pakistan.[7] Amongst the different ethnicities in Pakistan, Baluchis 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).[13] 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, no difference was found.[14] 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,] with age and BMI displaying a quantitative association.[15]

Control of Blood Pressure and Risk Attenuation (COBRA) and Control of Blood Pressure and Risk Attenuation-Bangladesh, Pakistan and Sri Lanka (COBRA- BPS) Trials provide an 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 deprived country. The largest hypertension study took place between 2004 and 2007, a cluster randomized controlled trial.[16] The Control of Blood Pressure and Risk Attenuation (COBRA) trial was conducted amongst 1341 patients, aged more than 40 years, with systolic blood pressure ≥140mm Hg and diastolic blood pressure ≥90mm Hg from 12 randomly selected communities, ranging 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 mm Hg in systolic BP levels in the HHE plus GP group over either of the two interventions alone or no intervention/usual care group.[16] 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 the governmental level in the management of hypertension in South Asian countries.[17]

In order to demonstrate a sustained effect of reduction in BP, a 7-year follow-up18 was conducted on the 1,341 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 2.1mm Hg lower BP than the no intervention/usual care group. Interestingly, the HHE plus GP intervention group had a greater decrease in LDL levels as compared to 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 utilising the current health care infrastructure without significantly altering the system logistics.[18]

The COBRA trial was conducted in the urban areas of Pakistan; however, the majority of the South Asian countries comprise of rural areas (Pakistan 64%, India 71%, Bangladesh 73% and Sri Lanka 85%).[19] 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.[19] It was aimed to pilot test the multicomponent intervention (MCI) in rural areas of Bangladesh, Pakistan and Sri Lanka. The MCI consists 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, and 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 ≥ 140mm Hg and diastolic BP ≥ 90mm Hg amongst 9 rural areas of Bangladesh, Pakistan and Sri Lanka. At three months' post-intervention, the results demonstrated a 4.5mm Hg drop in the systolic blood pressure out of overall pooled analysis among the three countries with a 10.5mm Hg of decline in systolic BP in comparison with 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, which is strongly adhered to by patients and is accepted by stakeholders.[19] The full scale cluster randomised controlled COBRA-BPS trial was conducted among 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.[20,21] These communities were assigned to either MCI or the usual care group (control group). A total of 2,645 adults with hypertension were enrolled.[21] the primary outcome was reduction in systolic blood pressure at 24 months. Follow-up at 24 months was completed for more than 90% of the participants. The mean systolic blood pressure (SBP) was 146.7mm Hg (MCI group) and 144.7 mm Hg (control group) at baseline. At 24 months, the mean SBP was reduced by 9.0 mm Hg (MCI group) and by 3.9 mm Hg (control group) and the reduction in SBP was 5.2 mm Hg higher with MCI. Blood-pressure control (<140/90 mm Hg) was better achieved in the MCI group than with the control (53% versus 44%). Similarly, all-cause mortality was lower (2.9%) in the MCI group versus 4.3% in the control group.[21] 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 longitudinal worsening over 7 years that was significantly associated with higher left ventricular mass index (LVMI) or the development of LVH among individuals with hypertension.[22] Already this landmark effort determined that for improved BP control, a home health education by trained government community health workers linked with existing public health care infrastructure and physician training can help attain sustained BP lowering as presented by decreased BP and other parameters.[21]

Such public work is critical for raising hypertension control awareness. Another national programme called HAMI (Hypertension Awareness and Management Initiative) has been established, which aims to increase awareness of this chronic disease in the general community via authentic and endorsed communication by key experts across the country. Similarly, in order to

control hypertension and the associated cardio-metabolic risk factors from a younger age, another expert group from Pakistan is conducting a trial to test the feasibility of a threefold health education programme - SHEPP (School Health Education Programme in Pakistan) in children and its efficacy on physical activity, diet and cardio-metabolic risk factors like BP, BMI and waist circumference. This trial is being conducted amongst children aged 9 to 11 years of age who go to school in low to middle income areas of Pakistan.[23] Two schools are enrolled with one school receiving the school health education programme (SHEPP) and the other continuing routine activity. This trial emphasises that SHEPP is a unique health education programme for children as it focuses on children while involving the parents and teachers into the behaviour change process. The group aims to replicate this trial as a large-scale implementation study in public sector schools also. Such important work generates a lot of potential avenues where hypertension can be controlled with cost-effective public health work.

With regard to private clinics where hypertension is managed in Pakistan, another expert group conducted a two-arm cluster randomised controlled trial 24 to study whether enhanced care at urban private clinics resulted in better control of hypertension and cardiovascular disease (CVD) risk factors, and treatment adherence. Twenty-six private clinics were randomised and included in the trial. Both the arms had enhanced screening and diagnosis of hypertension and related conditions, and patient recording processes. Intervention included a clinical care guide, additional antihypertensive drugs, a patient lifestyle education flipchart, associated training, and follow-up via cell phone. There was a significant BP reduction of 25.2 mm Hg in the intervention group versus only a 9.4 mm Hg reduction in the control group. This trial supports the scaling of an integrated cardiovascular disease-hypertension care intervention in urban private clinics in the areas that lack public primary care in Pakistan.[24]

However, even managing hypertension in the clinic has its challenges. In areas where hypertension is managed in the office, BP readings taken in the clinic do not correlate well with the gold standard 24 hour ambulatory blood pressure readings and are unable to overcome the white coat phenomenon.[25,26] Data from another group in Pakistan showed that the readings taken inside the clinic by the physician is around 10 mm Hg higher than the readings taken after the clinic visit is over.[27] This group suggests that since the BP is elevated upon meeting the physician, BP readings taken 15 minutes after the clinic were better since they correlated more strongly with the 24 hour ABPM readings.[28] Although widely recommended by the international guidelines, 24 hour ABPM monitoring is costly and not readily available in all medical centres of Pakistan. Therefore, an alternate test is necessary as a replacement for this expensive and cumbersome monitoring process. The alternate method proposed was post-clinic BP monitoring which is the reading taken 15 minutes after the patient has met the physician.[28] Another study showed that 3-hour ambulatory blood pressure (an abbreviated ABPM) study was an alternative to this gold standard test, as it correlated well with 24-hour ABPM.[29] Credible data now show that HTN is a problem that is starting in childhood, establishing itself in the adolescent age, with an overall pooled prevalence of 26.34%.[30] The age adjusted weighed prevalence in the adult population is an alarming 46.2%.[31] Women make more than 50% of our population, with prevalence of HTN that is more than that of men, and they face unique challenges in the access and reception of health care.[32] In the present time, it is therefore crucial to have commitment on the part of the stakeholders, a tactical document (guideline), registry and outcomes data. In the post COVID era, where health expenditure has been skewed towards the pandemic and natural calamities, we need to be even more efficient in the allocation of resource and planning.

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2.0 Blood pressure (BP)

When heart beats, it pumps blood round the body to provide 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.[1]

2.1 High Blood Pressure or Hypertension

Hypertension can be indicated when the blood pressure readings remain consistently 140mm Hg over 90mm Hg or higher for weeks examined during planned clinic visits as per protocol. Hypertension may also be present if just one of the numbers is higher than the threshold limit of either 140- or 90-mm Hg, taken according to a planned protocol of scheduled clinic visits. Continuously raised BP can cause complications that include but are not limited to the brain, heart, eyes, kidneys and the vasculature.[2]

A. **High normal BP (prehypertension):** BP higher than the threshold limit of either 130- or 80-mm Hg taken according to a planned protocol of scheduled clinic visits

.**B.** **High BP:** BP higher than the threshold limit of either 140- or 90-mm Hg taken according to a planned protocol of scheduled clinic visits.

C. **Target BP** is defined as the BP value below which there is benefit in terms of long-term outcomes

a) **Primary BP target:** <140/90 mm Hg is considered to be the primary target which all people other than the elderly should achieve.

b) **Secondary target:** <130/80 mm Hg is considered to be the secondary target which most people who are not frail or elderly can achieve.

c) **Target for the elderly:** <150/90 mm Hg is considered to be the target which most elderly people (>80 years of age) should achieve.

2.2 Signs and Symptoms of Hypertension

There are no usual signs and symptoms of Hypertension and therefore it is called the "silent killer". However, signs and symptoms can be observed with increasing complications associated with high BP like chest pain due to myocardial infarction, "thunderclap" headache associated with brain haemorrhage, paralysis or weakness of any part(s) of the body in case of a stroke etc.[3]

3.0 Risk factors for hypertension

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

3.1 Age

BP tends to rise with age. About 65 percent of people, who are of age 60 or older develop 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.[4]

3.2 Race/Ethnicity

High BP is more common in the African American adults than in the Caucasian or Hispanic American adults.[5] 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).[6]

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.[7] The term morbidly obese is for those individuals whose weight causes them to be at risk of increased morbidity and mortality despite excluding all other risk factors. So, obesity alone is a measure of adverse CV outcomes. Body mass index (BMI) is a measure of obesity. BMI classifications are based upon risk of cardiovascular disease. These classifications for BMI have been adopted by the WHO. The WHO guidelines for Asian individuals define overweight as a BMI between 23 and 24.9 kg/m^2 and obesity as a BMI >25 kg/m^2[8]

3.4 Sex

Before age 55, men are more likely than women to develop high BP. After age 55, women are more likely than men to develop high BP.[7]

3.5 Lifestyle Habits

The Unhealthy lifestyle habits that can raise BP include[7]:

A. Excess (salt) sodium or too little potassium
B. Lack of physical activity
C. Smoking
D. Drinking too much alcohol
E. 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. Having one or more close family members with high blood pressure, before the age of 60 means one has twice the risk of acquiring it also.[7]

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4.0 Measurement of blood pressure (apparatuses)

BP can be measured using variety of BP apparatuses like the mercury, aneroid and digital devices. 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[2,3]

BP readings produced by a conventional sphygmomanometer based on mercury, used to be considered as the golden standard, but as mercury is a toxic substance, these devices have been banned in most countries. These devices were extensively validated. 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 millimetres of mercury (mm Hg). 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.

A. Advantages of Mercury Sphygmomanometers

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

B. Disadvantages of Mercury Sphygmomanometers

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

4.2 Aneroid Apparatuses[2,3]

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 a cuff that is attached by tubes to a dial gauge marked in millimetres of mercury (mm Hg). 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.[4]

A. Advantages of Aneroid Sphygmomanometers

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

B. Disadvantages of Aneroid Sphygmomanometers

i. The aneroid gauge is a delicate mechanism. Special care should be taken to prevent accidental bumping or dropping of the gauge.
ii. 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.
iii. People with hearing or visual disabilities cannot use the device.
iv. Operating aneroid sphygmomanometers requires practice.

4.3 Automated Digital Sphygmomanometers[5]

Sociometric 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 BP. 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 occur. 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. In the recent past, the large scale randomized controlled trials have used automated devices, examples are the SPRINT and ACCORD trials.

A. Wrist blood pressure monitors

These are digital BP monitors that work similar to upper arm (brachial cuff) BP monitors but the results are not widely validated.6 It can be used by individuals, who find arm-based devices uncomfortable or painful. However, these are not recommended for everyone, due to the possibility of receiving false reading due to improper technique. BP monitors are very sensitive to body position and special care should be taken during their usage, in order to get accurate readings.

B. Advantages of automatic digital sphygmomanometers

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

C. Disadvantages of Automatic Digital Sphygmomanometers

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

4.4 Cuffless BP apparatuses

Cuff-based BP apparatuses may not be well-tolerated for repeated measurements, as is utilized with ambulatory BP monitoring. Furthermore, improper technique, including incorrect cuff placement or use of the wrong cuff size[6], may lead to erroneous readings, affecting diagnosis and management of hypertension. Compared with devices that utilize a cuff, cuffless BP devices may overcome challenges related to technique, tolerability, and overall utility in the outpatient setting. However, cuffless devices have several potential limitations that kerb its routine use for the diagnosis and management of hypertension.[7]
Cuffless BP devices have considerable potential for changing the diagnosis and management of hypertension. However, fundamental questions regarding their accuracy, performance, and implementation need to be carefully addressed before they can be recommended for clinical use.[8]

4.5 The preferred device for the measurement of BP

It is now recommended to use the digital automated oscillometer BP (AOBP) apparatus. It has emerged as a new gold standard. This allows for serial readings and does not need the staff to be there, which minimizes the alert response. Most devices can store readings and the more advanced apparatuses can be programmed to take timed readings, e.g., 3 readings in 5 minutes.

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5.0 Accurate method to measure BP

Adapted from the American Heart Association (AHA) guidelines of the management of hypertension.[1]

Step 1 Choose the right equipment: The following will be needed

a. Quality stethoscope
b. An appropriately sized BP cuff [table 1]
c. Validated and calibrated BP apparatus

Table-1: Selection Criteria for BP Cuff Size Measurement of BP in

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

Allow the patient to relax for 5 minutes before the first reading and sit upright with their upper arm positioned, so it is at 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 procedure.

Step 3 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 diaphragm 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 mm Hg above the person's normal BP reading. If this value is unknown, you can inflate the cuff to 160 - 180 mm Hg (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 mm Hg 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.

Cuff Inflation Hypertension

The muscular activity used to inflate the cuff can acutely raise the BP by as much as 12/9 mm Hg, 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 mm Hg 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 Measurement Methods and Significance

There are multiple types of BP measurements like office or clinic BP, ambulatory BP, nocturnal BP etc. Most researches have 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 predictive BP.[4] Interestingly, in the ASCOT BPLA trial, 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 haemodynamic response 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 trial 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. In an abstract presentation, Khan, et al demonstrated an average 20 mm Hg difference between the nurses' assessment room BP and the physicians' in-clinic BP, at a tertiary care hospital in Karachi. Large differences exist between-physicians 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 BP measurement by a physician cannot be avoided by repeated visits to the physician over a short time span. However, it can be reduced if a nurse performs the 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, that is the post clinic BP (PCBP), 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 PCBP 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, making it an important surrogate of mean daytime ABPM. Therefore, they suggested that post-clinic BP be employed for diagnosis and management of hypertension in the clinical setting. This suggestion is also viable in a health care set-up where ABP is not freely accessible and has larger financial implications for the population and health systems.

6.4 Ambulatory BP monitoring[11]

This method of BP measurement is the gold standard. It takes multiple readings; the studies deem anywhere from 70% to 85% readings to be successful to render the study interpretable. Different BP readings can be acquired. The overall mean reading is the average of all readings and the normal range is <130/80 mm Hg. The nocturnal BP is very important, as it is significantly associated with target organ damage. The night time normal value is <120/70 mm Hg. The night time periods show the dipping pattern that is normally at least 10% drop in BP at nighttime as compared to daytime BP (comparing means). The night time period also shows the morning surge, a period of vulnerability as strokes and MIs happen quite often at this time. The daytime mean normal BP is <135/85 mm Hg. BP variability of >15 mmHg is considered to be significant.

The ABP 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)

6.5 Home BP Monitoring (HBPM)

BP has largely been measured in the office. Today, we realise that BP measured in the office/ clinic setting can give erroneous readings in a significant number of patients when relying only on clinic BP for diagnosis.[1] Researchers have tried to find other ways (out-of-office) of measurement, i.e., home blood pressure monitoring (HBPM), ambulatory blood pressure monitoring (ABPM), etc.) to measure BP that would align with the correct reading when proper protocols of measurement are followed.[2] The false readings are encountered because every time a BP reading is taken in the office/clinic, it is subject to the alert response that produces the white coat hypertension (WCH) effect and also the masked hypertension (MH) effect is also noted which additionally produces a false reading.[3] The prevalence of WCH and MH is 23% (global range 15 – 30%) and 16%, respectively.[4] Compared with office BP, out-of-office BP has demonstrated a stronger association with hypertension

mediated organ damage and cardiovascular disease events.[5-7] Out-of-office or out-of-clinic BP measurements can be taken by ABPM or HBPM.

6.5.1 Advantages of HBPM [2,8-10]:

- It is more easily available for out- of -office assessments compared to ABPM.
- It gives multiple readings over intervals and long periods (over days).
- It is an excellent tool for the assessment of WCH and MH.
- It can be used to exclude false resistant hypertension (having resistant hypertension based on office BP but with controlled out-of-office BP).
- HBPM can empower patients with BP management, provided it is done with proper patient education.
- It can also help improve medication adherence.

6.5.2 Disadvantages of HBPM[2]:

- It has an up-front cost for the machine.
- It requires the subject to be literate and technologically savvy for self-interpretation.
- The standard HBPM devices cannot be used to assess nocturnal hypertension, although there are nocturnal devices that are being introduced into the market but are not mainstream yet.

6.5.3 Correct method of measurement[10,11]:

The method described below is also the recommended method for proper general BP measurement [Figure 1]. It is recommended that the BP should be taken under normal ambient conditions, with the patient instructed not to talk during the process of measurement:

A. The BP should be checked in both arms. The arm with the higher BP should be used.

B. The readings should be taken pre-meals on an empty stomach, without any stimulant like a caffeine drink, smoking, nicotine, e-cigarettes (vaping), etc., within 30 minutes of the measurement.

C. The morning reading should be taken within one hour of waking up, after using the toilet, and before breakfast. The evening reading should be before meals.

D. The patient should be rested for 5 minutes, and the patient's arm should be supported, e.g., resting on a desk/table.

E. The cuff should be placed directly above the antecubital fossa using the right- sized cuff. Extra-large cuffs do not come with most HBPM devices; therefore, they remain a problem to be solved, for individuals with extreme body habitus.[12] It is possible to adjust the cuff size after measuring the arm circumference by referring to standardised values. However, it is preferred to use the appropriate cuff.[13] In patients with obesity and conical upper arms, a wrist cuff device may be used to circumvent the problem. The use of wrist devices is not recommended otherwise due to a lack of validation studies and the possibility of false readings due to arm position variation and failure of the cuff to occlude the ulnar artery, which confounds the sensor result on the cuff.[11] If the wrist cuff is used at all, it should be under the strict supervision of the treating physician.

F. Ensure that the centre of the bladder is placed over the artery of the upper arm (there is a marker on the cuff for the artery). The length of the inflatable bladder should cover 80–100% of the arm circumference, and the width should be about half that of the length.[10] Ideally, the cuff should be applied over bare skin, but if one has light clothing and cannot remove it, then one can even apply it over thin fabric; however, this is not encouraged.

G. The preferred (ideal) HBPM period is 7 days, with 2 morning and 2 evening readings (taken 1 minute apart) performed each day.[14-16]

H. A minimum period of 3 days is also considered sufficient, as it manages to give a reading close to the true mean.[17, 18]

I. Once controlled, 1 to 3 days of readings (4 to 12 readings in total) is reasonable for follow-up.

J. For the purpose of monitoring, the average of all home BP readings should be calculated and used for therapeutic decision making.

6.5.4 Devices for HBPM:

Only validated devices should be used for HBPM. There are automatic devices that take a pre-set number of serial readings at programmed intervals, and this starts with a single press of the button by the patient. There are also semi-automatic devices that can do the same, but each reading requires a press of the button. Most devices have the capacity to maintain a log of the readings for record and later perusal by the physician. Although HBPM can also be done by a trained person who can take manual BP, but that brings in the alert response even at home, and therefore an automated unattended BP measure is recommended by the PHL. The BP Validated Device Listing (VDL) website lists validated BP devices that can be used.[19]

6.5.5 Indication for HBPM:

Multiple guidelines have accepted HBP as a supplement

Figure-1: Pictorial guidance to measure home blood pressure.

to clinic BP monitoring. Compared with clinic BP, home BP more accurately reflects the incidence of cardiovascular disease and major organ damage, in addition to mortality.[20] The indications for HBPM are as follows:

A. Diagnosis of hypertension.
B. White coat hypertension or white coat effect when the patient is already on pharmacologic intervention.
C. Masked hypertension.
D. Surveillance for compliance.
E. Assessment of resistant hypertension.

6.5.6 Interpretation of HBPM:

All the readings (both systolic and diastolic) are averaged. The average (mean) reading is used for diagnosis, treatment, and control.

6.5.7 Target BP for the diagnosis of hypertension:

HBPM values are lower than the clinic or office BP cut-off value. A cuff value of >135/85 is considered abnormal and can be used to diagnose hypertension.[21] This value correlates with office/clinic BP, which is 140/90 mmHg and 135/85 mmHg of mean ambulatory daytime BP. The same value is used in the follow-up visits to ensure control.

6.5.8 Limitations of HBPM:

Irregular heartbeat as in atrial fibrillation, is a cause of concern for the correct assessment of BP with HBPM. However, data suggest that taking three or more readings may circumvent this problem.[22] HBPM also has limitations when it comes to the assessment of nocturnal hypertension. Similarly, during pregnancy, when the volume in the body increases and there is a wide pulse pressure, the validity of the standard HBPM device becomes less reliable. Research is needed in this area for more robust evidence.[11]

6.5.9 Importance of HBPM for Pakistan:

The BP control in Pakistan is low at around 12.5%.[23] Among patients who had hypertension in rural Punjab, 62.3% were aware of having high BP, and of these, 75.3% were already on treatment. BP was only controlled in 22.3% of all patients with hypertension.[24] This is a cause for concern, and self-monitoring is the way to go to tackle the problem. HBPM empowers individuals to measure BP,

Days	Morning BP		Average 1 (A1)	Evening BP		Average 2 (A2)	Average A1+A2/2
	BP1	BP2	BP1+BP2/2	BP3	BP4	BP3+BP4/2	
1							
2							
3							
Minimum readings over 3 days							
4							
5							
6							
7							
Example	130/80	135/85	132.5/87.5	140/90	140/85	140/87.5	136.25/87.5
Grand average reading (average the readings in the last right column)							
Target BP <135/85 mmHg							
If measured average BP > 135/85 mmHg			Consult physician				
If measured average BP < 135/85 mmHg			Continue therapy as per advice				

and once high BP is noted, self-awareness is achieved. This allows for self-referral to a health care facility and the start of treatment after a thorough assessment.

6.5.10 Home BP Monitoring Chart:

Do not speak during the measurement. Take three readings for the first time, discard the first reading, and average the other two readings. For the remainder, average the two readings. The interval between the two readings should be one minute. Use the same device and ideally measure at the same fixed time of the day, e.g., 8 a.m. in the morning and 8 p.m. on the same day. It is up to the patient to decide the most convenient time and follow it. There will be 12 minimum readings over 3 days or 28 readings over 7 days.

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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 ischaemic heart disease death for both men and women.[1]

7.1 Treatment threshold and target values

A. Optimal systolic BP target

Data on optimal BP treatment targets, particularly for systolic blood pressure, were largely based on metanalyses 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 mm Hg and/or diastolic BP 90-99 mm Hg) have not been shown to reduce mortality or morbidity in RCTs. Treatment caused 9% of patients to discontinue medication due to adverse effects. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms.[2]

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.[3]

B. Addressing the lower BP targets

HOPE 3 trial:[4] This trial enrolled 12, 705 patients, 46% females with a mean age of 65.8 years and 15% of the study population was South Asians. Included were men ≥55 years, women ≥65 year with at least one of the following CV risk factors for men and two for women:

- Elevated waist-to-hip ratio
- History of a low level of high-density lipoprotein cholesterol
- Current or recent tobacco use, deglycation
- Family history of premature coronary disease
- Mild renal dysfunction

The baseline BP was 138.1/81.9 mm Hg and the BP decrease was 6/3 mm Hg. A fixed-dose combination of candesartan 16 mg + 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.

C. The SPRINT trial and its implications in the setting of lower goals[5]

The SPRINT trial showed that intensive BP control to SBP <120 mm Hg results in significant cardiovascular benefit among high-risk patients of 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 9,361patients were followed-up for the duration of 5 years (median 3.26 years) with mean age ≥50 years, presenting hypertension with SBP ≥130 mm Hg and at least one risk factor for heart disease:

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

The trial was terminated earlier than the planned time because of significant 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 indicated 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 was a landmark trial and resulted in a paradigm shift in the management of patients with hypertension, when 130/80 mmHg was used as one of the targets for BP control by different guidelines.

D. 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 oscillometer measurements without an observer in the room. The relationship of this research-grade methodology to routine BP measurements is not known.6 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.[6]

E. BP target of <150/90 for ages >60 years or 80 years

The JNC 8 guideline suggested a target of <150/90 for age >60 years, whereas this target is used by the NICE and ESC guidelines for age 80 years or above. This evidence comes from multiple trials, which include HYVET[7], Syst-Eur[8], SHEP[9], JATOS[10], VALISH[11] and Cardio-Sis trials.[12] Moderate to high quality evidence that shows that treating the general population aged ≥ 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 ≥ 80 years in HYVET, 70–< 85 years in VALISH, 65–85 years in JATOS, ≥ 60 years in SHEP and Syst-Eur, and ≥ 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[13] 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) was 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.[14] Therefore it is recommended that people over the age of 80 years BP less than 150/90 mm Hg as target.

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8.0 Diagnosis of hypertension

PHL endorses Hypertension Canada's[1] diagnostic approach and proposes the algorithm [figure 2]:

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

B. Visit 1: If SBP is >140 mm Hg and/or DBP is >90 mm Hg 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.

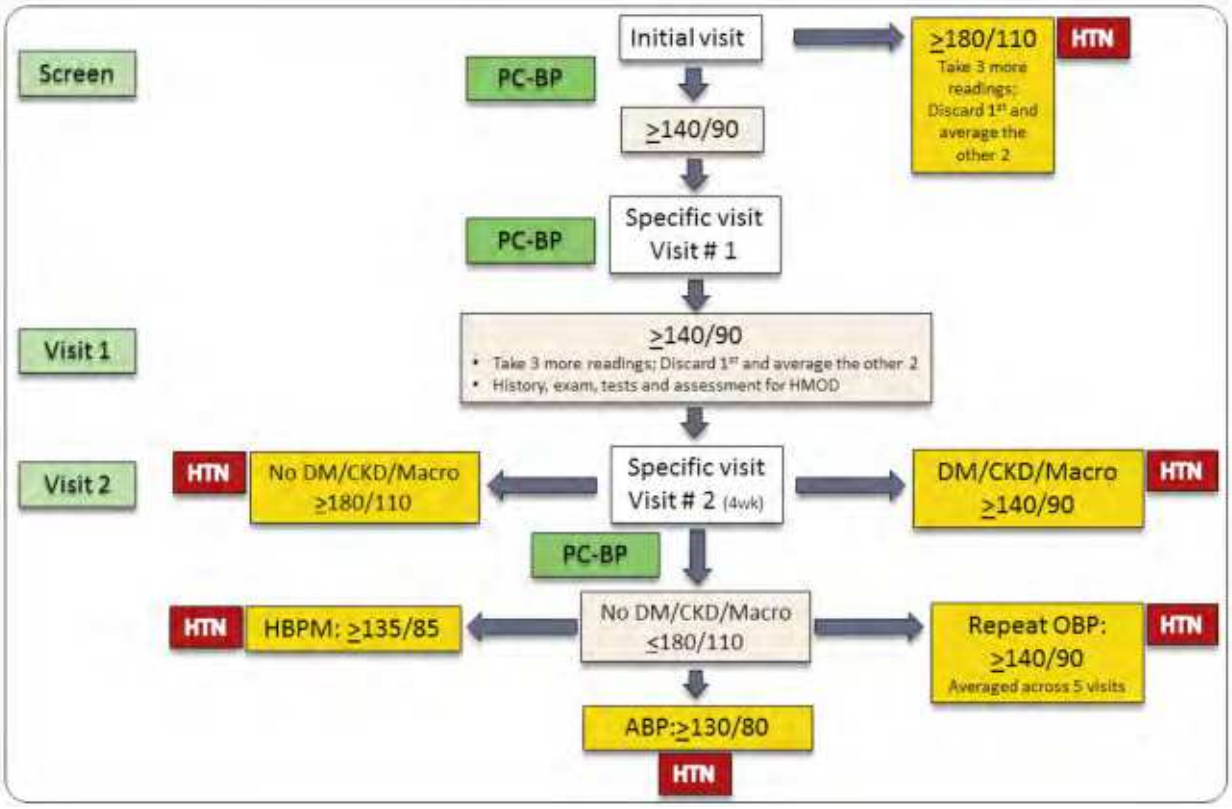

Figure-2: Algorithm for diagnosis of hypertension.

PC-BP: post clinic BP, HMOD: hypertension mediated organ damage, OBP: office BP, HBPM: Home BP monitoring, ABP: Ambulatory BP monitoring, Macro: macro-vascular disease

Take a history, perform a physical examination, and assess for H.M.O.D. Initial tests should be ordered on this visit.

C. Visit 2 (4 weeks): If there is macrovascular disease, DM and/or CKD, and BP SBP is >140 mm Hg and/or DBP is >90 mm Hg then diagnose HTN. If no macrovascular disease, DM and/or CKD and SBP is >180 mm Hg and/or DBP is >110 mm Hg then diagnose HTN. If no macrovascular disease, DM and/or CKD, and BP SBP is <180 mm Hg and/or DBP is <110 mm Hg then evaluate further on a subsequent visit for Office BP, HBPM or ABP.

D. Repeat Office BP: If the average of 3 readings of BP>160/110, or BP >140/90 averaged across 5 visits diagnose HTN.

E. Home BP: If the SBP is ≥135 mm Hg or the DBP is ≥ 85 mm Hg diagnose HTN. If the Average home BP is < 135/85 mm Hg, it is advisable to either repeat home monitoring to confirm or perform ABP to see if BP <130/80 mean awake ABP <135/85.

F. ABP: If BP >130/80 (overall), >135/85 (daytime).

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9.0 Diagnostics work-up[1]

Laboratory measurements should be obtained for all those patients who have been newly diagnosed with 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 HMOD. 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 HMOD for the level of BP, or historical or clinical clues that support a secondary cause. For resistant or refractory hypertension (defined as uncontrolled BP despite use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and a mineralocorticoid receptor antagonist, at maximal or maximally tolerated doses),[2] a referral to a specialist is recommended.

9.1 Hypertension mediated organ damage (HMOD) [table 3]

Hypertension is a major cause of cardiovascular disease and was recently put forward as the leading risk factor for global disease burden.[3] Long-term hypertension induces damage to the vasculature and myocardium,[4] as well as to the kidneys.[5] The principal focus is on the arterial vessel as the main organ involved in hypertensive patients. Heart disease may be considered as one of the principal consequences of vascular dysfunction discussed extensively in literature.[6]

Table-2: Diagnostic work-up needed for HTN

Basic Test: baseline assessment risk profiling	Additional test In difficult to control BP situations
Complete blood count	Thyroid stimulating hormone (TSH)
Fasting blood glucose	Echocardiogram
Serum creatinine with eGFR*	Urine albumin creatinine ratio
Sodium, Potassium	Uric acid
Lipid profile	
Urine detailed report	
Electrocardiogram (ECG)	

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

Table 3. Hypertension mediated organ damage (HMOD) Adapted from CHEP 2011 guidelines. Hypertension Canada.

Table-3. Hypertension mediated organ damage (HMOD)

Cerebrovascular disease	Transient ischaemic attack, Ischaemic or haemorrhagic stroke and 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	Intermittent claudication Ankle brachial index <0.9#

Campbell NR, Poirier L, Tremblay G, Lindsay P, Reid D, Tobe SW, Canadian Hypertension Education Program. Canadian Hypertension Education Program: the science supporting new 2011 CHEP recommendations with an emphasis on health advocacy and knowledge translation. Canadian Journal of Cardiology. 2011 Jul 1;27(4):407-14.

*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 50 years age, every diabetic over 50 years, and all patients over 70 years.

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

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10.0 Why treat blood pressure?

Lowering BP with drug therapy provides benefit. Although, when there is no HMOD or cardiovascular risk factors and mild hypertension the benefit is not that clear, but as risk factors are added to the history benefit 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] In a study[4] of electronic health records of 38, 286 low-risk patients with mild hypertension, no evidence of an association was found between exposure to antihypertensive treatment and mortality or CV disease. There was evidence that treatment may be associated with an increased risk of adverse events with number needed to harm at 10 years [NNH_{10}], 41), syncope (HR, 1.28; 95% CI, 1.10-1.50; NNH10, 35), electrolyte abnormalities (HR, 1.72; 95% CI, 1.12-2.65; NNH10, 111),and acute kidney injury (HR, 1.37; 95% CI, 1.00-1.88; NNH_{10}, 91).

The SPRINT trial had a large number of people with mild hypertension at recruitment, but all participants were considered to be at high risk of CVD and 90% were already undergoing treatment.[5] 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% (intermediate risk).[6,7] So, for the treatment of mild hypertension the CV risk needs to be considered. For patients with mild hypertension, no HMOD and low CV risk, it is prudent to initiate and maintain non-pharmacologic intervention (NPI) and planned follow-up. It is imperative that NPI be taken as a serious tool and active assessment at each visit to be part of follow-up. Target out comes parameters like weight loss, waist circumference, lab data etc.

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11.0 Hypertension (Simple and with compelling indications)

11.1 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.

11.2 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-blockers 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.

The PARADIGM HF trial showed that LCZ696 (sacubitril-valsartan) was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure.[2] Therefore, in HF and hypertension, ARNI may be considered a frontline therapy. The PARAMETER trial demonstrated antihypertensive effect of ARNI for the first time, demonstrating superiority of sacubitril/valsartan over Olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in the elderly patients with systolic hypertension and stiff arteries.[3]

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

S No	Conditions	Drugs
1.	Heart failure	• Diuretics • Beta blockers • ARNI or ACE inhibitors/angiotensin receptor blockers • Aldosterone antagonist
2.	Myocardial infarction	• Beta blockers • ACE inhibitors
3.	Diabetes Mellitus	• ACE inhibitors/Angiotensin receptor blockers
4.	Chronic kidney disease	• ACE inhibitors/Angiotensin receptor blockers

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;42:1206-52.

11.3 Threshold for diagnosis and treatment [table 5a, 5b]

The JNC 8, ESC, BHS, CHEP and other international guidelines have up till now recommended <140/90 mm Hg as threshold for treatment. The ESC 2018 guidelines have recommended achieving 130/80 mm Hg, where possible after reaching the goal of 140/90 mm Hg.[4] As stated earlier, it has been known that the risk of adverse outcomes goes up as the SBP rises above 115 mm Hg.[5, 6] The SPRINT trial[7] showed that lowering BP to tight control <120/80 mm Hg accrued benefit for the patient, although at an increased cost of side effects. The AHA 2017 guidelines[8] have lowered the threshold for diagnosis to 130/80 mm Hg. 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. Subsequently, three readings were taken and averaged out.[4] It was noted that this measurement of BP was not the same as office BP measurement. 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,[9] showed that unattended and attended office BP measurements achieve comparable results, if

Table-5a: International Hypertension Guidelines: Classification of Hypertension.

Stage	BP values mm Hg	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 I	Grade 1	Grade 1	Stage I	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 HMOD	>180/110	HTN crises	Grade 3	Grade 3	HTN crises	HTN crises >180/120

The International Society of Hypertension (ISH) guideline 2020 maintains, normal <130/85; high normal 130-139/85-89, grade 1 140-159/90-99 and grade 2 >160/90-99 mm Hg. (Unger T, et al. Hypertension. 2020; 75:1334-1357.

Table -5b: Classification, lifestyle modification and therapy.

Stage	BP values	Life style Modification	Follow up	Drug Rx
Optimal	<120/80	Step 0	Follow-up 2 years	None
Elevated	120-129/80-84	Step 1 then step 2	Follow-up 1 year	None
Pre-HTN	130-139/85-89	Step 1 and 2 together	Follow-up 1 year if no CV risk or CVD	None
Pre-HTN	130-139/85-89	Step 1 and 2 together	Follow-up 6 months if 10year CV risk of CVD>10% or CVD	1 drug Rx
Stage 1	140-159/90-99	Step 1 and 2 together	Follow-up 4 - 6 weeks	2 drug Rx
Stage 2	160-179/100-110	Step 1 and 2 together	Follow-up 4 - 6 weeks	Mild to moderate doses
Stage 3	180/120 No HMOD	Step 1 and 2 together	Follow-up 1 - 2 weeks	Moderate doses of 2 Drug Rx
HTN crises	>180/120 and HMOD/Acute injury	Step 1 and 2 together	Follow-up 1 week	Escalate Rx

measurements take place at a familiar general practitioner's office. On the contrary, Agarwal10 showed through a prospective trial that 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 protocols.

A. 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 mm Hg or more. The group's median 10-year Framingham risk score was ≤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.[11]

The STEP trial showed that in older patients with hypertension, intensive treatment with a systolic BP target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to less than 150 mm Hg.[12] 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[13] and heart failure in non-diabetic patients.[14] A meta-analysis conclusively demonstrates that a more intensive BP control strategy is superior to a less intensive control strategy for prevention of stroke, HF and MI. They also found a significant benefit, albeit not conclusive, of a more intensive over a less intensive strategy for prevention of cardiovascular death.[15] 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, presence of HMOD and also the ability of the healthcare infrastructure to provide care for gradual tight control in a safe manner.

B. PHL recommendation [figure 3]

i. The PHL taking the above into account sets 130/80 as a secondary target and BP <140/90 as the primary target for treatment.

ii. Treatment groups to be divided into two groups.
a) Group 1 is with no CVD, DM or CKD or 10-year risk of CVD <10%.
b) Group 2 has CVD, DM, CKD or 10-year risk of CVD >10%.

iii. Group 1 would be subjected to heart healthy life style meditation. On the other hand, group 2 would be given lifestyle meditation, but if not controlled in 6 months would be started on–medical therapy.

iv. The target would be primary target <140/90 mm Hg, secondary BP target <130/80 mm Hg.

v. For all other categories (see table 5), if the patient has at least one risk factor the target of BP lowering should be < 130/80 mm Hg.

vi. For those with hypertension and no other risk factor a target of < 140/90 mm Hg.

vii. For those who are very elderly (age >80 years), the target would be <150/90 mm Hg.

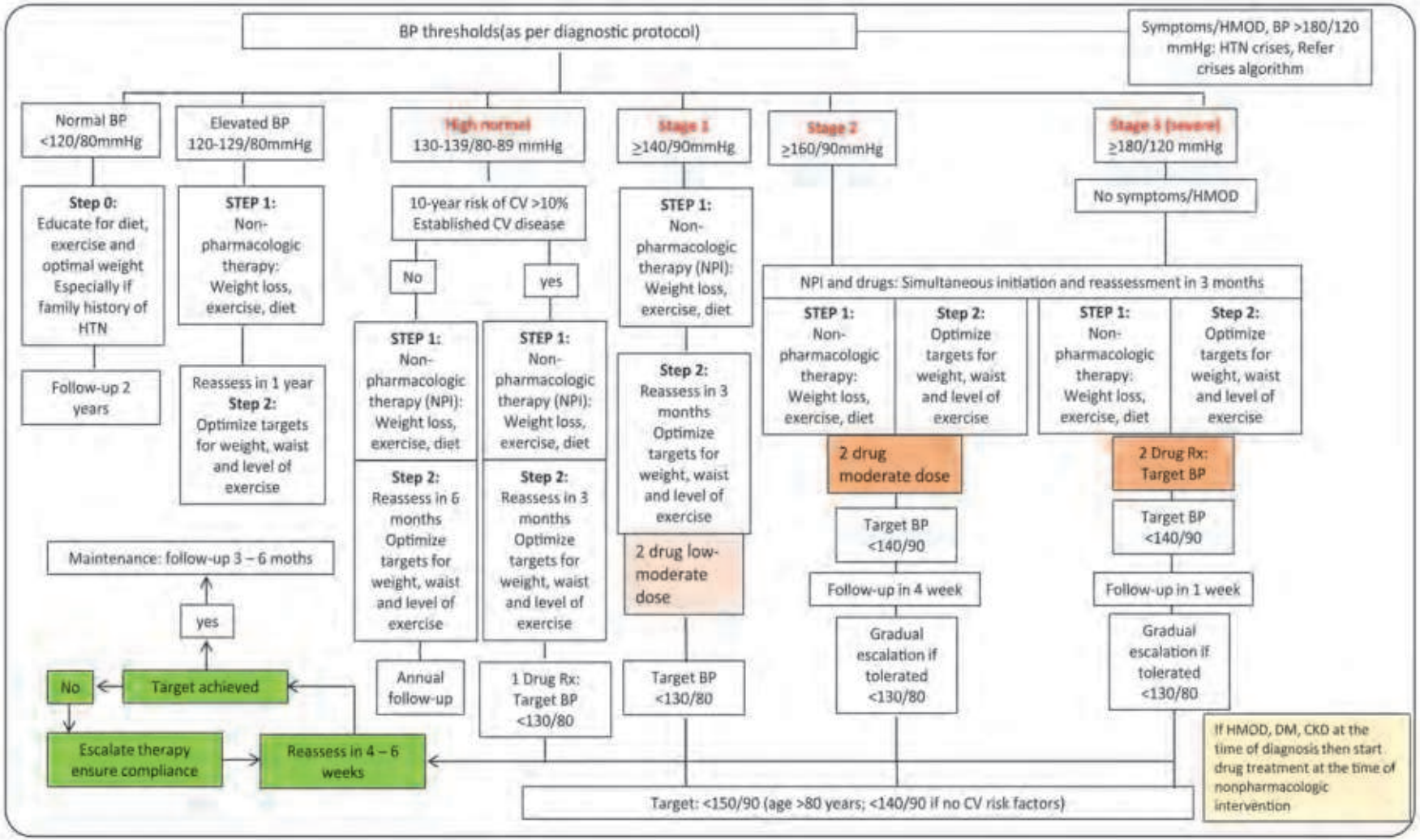

Figure-3: Blood pressure thresholds for the treatment and plan for follow-up.

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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 cardiometabolic conundrum. Furthermore, the aim is to prevent the development of atherosclerotic cardiovascular disease, which now includes stroke. The PHL endorses the ACC/AHA guidelines[1] for the assessment of cardiovascular risk.

i. 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.
ii. 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.
iii. Statin therapy is 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 CV event has been used. The CV event can be 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

i. 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.

ii. For patients with low 10-year risk (< 7.5%), assessing 30-year or lifetime risk is recommended in patients 20-59 years old.

iii. 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 measurable and potentially modified risk factors 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, women, young and old. More recently, McGorrian et al.[4] modified the INTERHEART risk score into the INTERHEART Modified 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 each one can be accessed via the internet as there are applications for both cell phones and 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 benefit in primary CVD prevention. Although aspirin is inexpensive and widely available, especially in developing countries like Pakistan, there is lack of evidence that the benefit 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 final 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] results 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 ischaemic 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 included 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 ≥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] The decision to start low-dose aspirin for the primary prevention of CVD in adults aged 40 to 59 years, who have a >10%, 10-year CVD risk, should be an individual one, and no low-dose aspirin use for the primary prevention of CVD in adults aged 60 years or older.[11] The clinical benefit of low-dose aspirin for primary prevention is marginal and must be carefully balanced against the well-known excess risk of major bleeding.

13.1 Recommendations

PHL recommends: Aspirin to be used only for established CV disease or patients at high risk for CV disease as estimated through a risk calculator (> 10%, 10-year CVD risk) or someone with a CAC score >100.

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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 (dyslipidaemia, 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 1or 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 therapy.

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 cutoff

Table-6: Non-pharmacologic Therapy: Stepwise approach

Variable	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^2 [underweight] 18.5 - 23 kg/m^2 [normal] 23-27.5 kg/m^2 [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, dyslipidaemia patients	Educate	Recommend	Enforce
Salt	<100mmol/d, 2.4g Na*, 6gm NaCl, (1 teaspoon salt/day)	Educate	Recommend	Enforce
Exercise	Aerobic exercise for 30 mins most days/week	Educate (home training)	Recommend (training advice)	Enforce (supervised programme)
Sleep	> 6 hours	Educate	Recommend	Enforce (sleep specialist)
Exercise	Aerobic exercise for 30 mins most days/week	Educate (home training)	Recommend (training advice)	Enforce (supervised programme)
Depression /Anxiety	Screen using Patient health questionnaire (short version)	Educate	Recommend	Enforce
Smoking	Quit	Quit	Quit/alternatives	Smoking cessation programme
Alcohol	Quit	Quit	Quit	Quit

Note: Sedentary behaviour is a person who takes less than 5000 steps in a 24-hour period. (Sports Med. 2004;34:1-8).
It is recommended to follow the "some is better than none" approach, as every step counts and goes towards overall better outcomes. (Ramsey KA, et al. Lancet Healthy Longev 2021; 2: e764–72)

of waist circumference of < 90 cm for men and < 80 cm for women. Cut-off points vary considerably between countries and the variations are based greater on waist circumference than for waist–hip ratio. Along with that the cut-off points 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, dyslipidaemia and clustering of risk factors all increase with increasing BMIs even at indices below the international current cut-off point for overweight (i.e., 25 kg/m^2).

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^2 or higher, representing increased risk, and 27.5 kg/m^2 or higher as representing high risk. The suggested categories are as follows: less than 18.5 kg/m^2 underweight; 18.5–23 kg/m^2 increasing but acceptable risk; 23–27.5 kg/m^2 increased risk; and 27.5 kg/m^2 or higher, high risk.[6]

15.2 Exercise [Table 6 and 7]

Aerobic exercise is universally recommended as initial lifestyle therapy for individuals with hypertension as it lowers BP about 5–7 mm Hg among adults diagnosed with hypertension. A combination of 30 min or more per day of moderate intensity aerobic exercise on most, preferably all days of the week is recommended. However, dynamic resistance exercise for 2 to 3 days per week with the total duration of 150 min or more per week is preferred. The notable emphasis comes in on the inclusion of dynamic resistance exercise in combination with aerobic exercise.[7] 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 exercise programme or competitive athletics, but should be evaluated, treated, and monitored closely. Comorbid conditions such as diabetes, ischaemic 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.O2R) 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.[8]

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.O2R)
- **Time:** ≥ 30 min of continuous or accumulated physical activity per day
- **Type:** primarily endurance physical activity supplemented by resistance exercise.

15.3 Complementary and Alternative Medicine Yoga

A recent meta-analysis was conducted of 17 randomised and non-randomised trials of yoga and hypertension.[9] Results showed that yoga had a modest effect on both SBP [-4.17 mm Hg] and DBP [-3.26 mm Hg]. There was

Table-7: Exercise capacity assessment

	Minimum Cardiovascular Benefit	Aerobic limit (level 1)	Aerobic threshold (level 2)	Severe exercise (level 3)
Borg scale RP	11 (fairly light)	(Between somewhat hard and hard)	17 (Very hard)	18-20 (Extremely hard to exhaustion)
%VO2 max	50%	60 TO 65%	80 TO 85%	> 85%
% HR max	70%	75 TO 80%	90 TO 92%	95 TO 100%

National Council on strength and fitness.
https://www.ncsf.org/pdf/ceu/relationship_between_percent_hr_max_and_percent_vo2_max.pdf

Borg Scale of perceived Exertion		
6	No exertion	How you feel when watching TV or reading a book
7	very, very light	Little or no effect
8	Very light	
9		
10	Fairly light	
11		
12	Somewhat hard	Target range: Ho you should feel with most exercise or activity.
13		
14		
15	Hard	
16		
17	Very hard	How you felt with the hardest work you have ever done
18		
19	Very very hard	
20	Max exertion	Don't work this hard

Borg G.A Psychophysical bases of perceived exertion. Medicine and Science in Sport and Exercise. 1982; 14:377-381

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 mm Hg and-6.14 mm Hg] 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.[10]

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.[11] It needs to be remembered that BP lowering effect of weight loss has a lag time and immediate drop should not be expected. It happens after a sustained weight loss.

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 2.4 grams Na+, 6 grams salt (1 teaspoon); this may lower BP by 2-8 mm Hg.[12,13] Some individuals may require 1.5 grams of Na+. The effect of sodium chloride is particularly important in individuals who are middle-aged to elderly with a family history of hypertension.[11] 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.[11]

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 increased risk for heart disease, and continued smoking can be a major risk factor for recurrent heart attacks.[14] It is the need of the day to have smoking cessation programmes in hospitals where a concerted effort can be made to ensure that current smokers quit the habit. 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 counselling and nicotine addiction programs should focus on young women.[15]

There is an association between the use of smokeless tobacco and hypertension in the general population and in diabetic patients.[16] This association is linked to the nicotine and salt content of smokeless tobacco and also to renin-aldosterone suppression due to the liquorice contained in chewing tobacco (and its active ingredient,

Table-8: Heart Healthy Life Style

	JNC	AHA	PHL	BP reduction
Reduce weight	Maintain normal weight (BMI 18.5-24.9 kg/m^2)	Attain BMI<25 kg/m^2	18.5-23 kg/m^2 Waist: 90 cm men, 80 cm 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+. 6g NaCl)	65 mmol/d (1.5g Na+. 3.8g NaCl)	≤100 mmol/day (2.4g Na*, 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) OR25 minutes of vigorous aerobic activity x 3 days/week (total of 75 minutes): or a Combination of moderate- and vigorous-intensity aerobic activity ANDModerate to high Intensity muscle- strengthening activity 2 days/week for additional health benefitsFor BP lowering: 40 mins of moderate to vigorous exercise 3-4 days/week	4 - 9 mm Hg
Stress	None given	None given	Avoid stress/manage stress	Not assessed
Potassium intake	None given	120 mmol/day	120 mmol/day	Variable
Alcohol	≤2drinks/d for men; ≤1 drink/d for women	Same	No alcohol	2 – 4 mm (if alcohol reduced

glycyrrhizin acid), which may have a causative role in tobacco chewers' hypertension.[17]

15.7 Nutrients, vitamins and fish oil

Controlling blood pressure ideally to less than 130/80 mm Hg is vital for long-term circulatory health. While medication is often needed but 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.18 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.[18]

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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, methyldopa etc. For rapid lowering of BP drug administration for hypertensive emergencies requires intravenous administration, nitroprusside, hydralazine, glyceryl trinitrate (GTN), esmolol etc.[1,2]

16.1 Drug Therapy for Hypertension [table 10, figure 4]

The treatment of hypertension entails an algorithmic approach to makes it simple to follow, that is universal and has better compliance. After a change from ABCD to ACD-SDB approach, the current guideline continues with the same approach but defines the first line therapy as any of the first three that is ACE inhibitor/ARB, CCB and diuretic.

It is recommended to start with a combination of low doses or moderate doses of the first line drugs, depending on the level of BP. The diuretic preferred is a long-acting diuretic like chlorthalidone or indapamide [thiazide like diuretic]. Thiazide type diuretic like hydrochlorothiazide are short acting diuretics, and if used should be used with a longer acting category of the other drug. 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] ACE inhibitors and ARBs effectively lower BP through inhibition of the renin-angiotensin system and are equally recommended as first line medications in the treatment of hypertension in most leading guidelines.[1,4]. There is extensive evidence that blood pressure lowering by renin-angiotensin system inhibition using these drug classes improves cardiovascular outcomes, as shown in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and HOPE (Heart Outcomes Prevention Evaluation) trials as well as in meta-analyses and across a global network of 8 large observational databases.[5] systematic reviews[5] The LEGEND-HTN (Large-scale Evidence Generation and Evaluation across a Network of Databases for Hypertension) study, sought to compare the real-world effectiveness and safety of ACE inhibitors and ARBs for the first line treatment of hypertension across a global network of 8 large observational databases.[5] In this large-scale observational study of over 3 million patients, initiating antihypertensive treatment with ACE inhibitors or ARBs across 8 databases worldwide, no statistically significant difference in the effectiveness of ACE inhibitors versus ARBs on AMI, HF, stroke, or composite CV events was found, while ARBs had a better safety profile with lower risks for acute pancreatitis, angioedema, cough, and GI bleed. This study represents the largest head-to-head comparison of ACE inhibitors with ARBs to-date and supports the preferential prescribing of ARBs over ACE inhibitors.

The LEGEND-HTN showed that ARBs do not have significantly different effectiveness in long-term cardiovascular outcomes compared with ACE inhibitors and have a better safety profile. The most dreaded side effect of ACE inhibitors being angioedema; Banerji, et al, identified 0.07% incidence of ACE inhibitor induced angioedema within 1 month of prescription and a 0.23% incidence during the first year. Incidence of angioedema was relatively constant annually over the subsequent 4 years (0.10% to 0.12%).[6] Makani, et al, noted that

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

Class	Drug	Dose mg	Frequency / Day	Comments
ACE inhibitors (ACEI) A	Captopril Enalapril Eosinophil	12.5 – 150	2 or 3	Increased risk of hyperkalaemia, 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.
	Lisinopril	5 – 40	1 or 2	
	Perindopril	10 – 40	1	
	Quinapril	10 – 40	1	
	Ramipril	4 - 16	1	
	Trandolapril	10 – 80	1 or 2	
		2.5- 10	1 or 2	
		1 – 4	1	
Angiotensin Receptor Blockers (ARB) A	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 Losartan	150 -300	1	
	Olmesartan	50 – 100	1 or 2	
	Telmisartan	20 – 40	1	
	Valsartan	20 - 80	1	
Calcium channel blockers Dihydropyridines C	Amlodipine	2.5 -10	1	Avoid use in HFrEF; amlodipine or felodipine may be used if required. Associated with dose-related pedal oedema, 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 C	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 & verapamil (CYP3A4 major substrate and moderate inhibitor).
	Diltiazem SR	180 – 360	2	
	Verapamil	120 – 480	3	
	Verapamil SR	240 – 480	1	
Thiazide type or thiazide like Diuretics D	Hydrochlorothiazide	12.5 – 50	1	Monitor for hyponatraemia and hypokalaemia, 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 antagonism S	Spironolactone	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

Table-9b: Drugs for the treatment of hypertension (5th, 6th and 7th line drugs)

Class	Drug	Dose mg	Frequency /day	Comments
Beta blockers-cardio selective	Atenolol Bisoprolol Metoprolol tartrate Metoprolol succinate	25 – 100 2.5 – 10 100 – 400 50 - 200	1 to 2 1 1 to 2 1	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
Beta blockers-cardio selective and vasodilatory	Nebivolol	5 – 40	1	Nebivolol induces nitric oxide–induced vasodilation. Avoid abrupt cessation.
Beta blockers-non cardio selective	Nadolol Propranolol IR	40 – 120 160 - 480	1 2	Avoid in patients with reactive airways disease. Avoid abrupt cessation.
Beta blockers-combined alpha and beta-receptor	Carvedilol Labetalol	12.5 – 50 200 – 800	2 2	Carvedilol is preferred in patients with HFrEF. Avoid abrupt cessation
Alpha-1 blockers	Doxazosin Prazosin	1 – 8 2 - 20	1 2 or 3	Orthostatic hypotension (older age).They may be considered with concomitant BPH
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.

incidence of angioedema with ARBs was less than half of that with ACE inhibitors and not significantly different from placebo. Incidence of angioedema was higher in patients with heart failure compared to those without heart failure with ACE inhibitors and ARBs.[7] Furthermore, Banerji, et al[6] noted that patients with ACE inhibitor induced angioedema were more likely to have a history of nonsteroidal anti-inflammatory drug allergy compared with patients who did not develop angioedema (7.1% vs 4.2%, P<.001). Currently, most guidelines are recommending ACE inhibitors and ARBs as first line treatment. Given the overall lifetime cost, adverse effects profile and sustained availability, the guideline leaves the choice of first line component therapy for initiation to the discretion of the physician, with consideration of the above. It is imperative to ensure compliance of the drug and control of BP.

Thiazide-like diuretics have greater protective effect against cardiac events than thiazide-type diuretics, especially on heart failure, suggesting that preferential use of thiazide-like diuretics over thiazide-type diuretics may result in greater cardiovascular benefits in hypertensive patients.[8]

Current global guidelines recommend the use of beta blockers for patients with CHF, CAD, and AF. Within its class, nebivolol has shown beneficial effects on central aortic pressure, endothelial function and aortic stiffness. Nebivolol has additional vasodilating effects, which may be useful in hypertensive patients with CAD or with erectile dysfunction. It has a good tolerability profile which makes it safe to use in patients with metabolic abnormalities (such as diabetes or dyslipidaemia) or chronic obstructive pulmonary diseases.[9] Sexual dysfunction is more prevalent in hypertensive individuals compared with the normotensive population, and often causes low adherence to or discontinuation of antihypertensive treatment.10 In contrast, other agents, conventional β-blockers, may induce or worsen sexual dysfunction in treated patients, ACE inhibitors, ARBs, CCBs or vasodilating beta blockers potentially exert neutral or

Table-10: Drug treatment of hypertension with compelling indications

Drugs	Priority	DM	CKDPre-HD	CKD HD	Proteinuria**	CVD	CHF/low EF
ACEi/ARB	1st line drugs (Equal weightage)	1	1	3	1	1	May initiate
CCB-DP		2	2	2	-	3	5
Thiazide like diuretic		3	3	-	3	4	4
ARNI	S	-	-	-	-	-	1 (or shift from ACEi/ARB)
Resistant HTN	Referral						
Spironolactone Eplerenone*	2nd line drug	4	4	4	4	5	5
Doxazosin	3rd line drug	5	5	5	5	6	6
Refractory HTN	Referral						
Bisoprolol# (Beta blockers)	4th line drug	6	6	1	6	2	2
CCB-NDHP*#	R	-	R		2		
Furosemide*^	R	-	R	-	-	-	6 or higher depending on volume
Hydralazine	5th line drug	7	7		7	7	7

Numbers 1, 2, 3, 4, 5, 6 are given in order of priority of usage, 1 being first; *drugs can replace main line drugs; ^use where fluid clearance is required for fluid overload; # may be used if concomitant issues of arrhythmia; R is replacement therapy; S is special consideration; for Beta blockers other drugs like nebivolol, carvedilol, etoprolol, atenolol may be considered depending on the medications; replacement medication can also be used in cases of side effects of mainline therapy e.g., CCB-NDHP for beta blockers in asthma patients. The role of Lasix in HF/low EF may be variable; Carvedilol preferred in HTN with CHF. CVD includes coronary artery, and neurovascular diseases, e.g., MI, stroke etc. CKD^^ is divided into pre-dialysis and patients on HD. ** SGLT2 inhibitors delay progression of proteinuria in CKD and may be an add on therapy.

beneficial effects. In trials nebivolol did not affect serum glucose in either diabetic or nondiabetic patients11 and had fewer new onset diabetes cases during treatment versus placebo (1.8 vs 2.1%).[12]

The control of BP to higher targets requires use of up to three or more drugs[13], which will include the first choice of an ACD combination. The PATHWAY 2 trial[14] has shown the effectiveness of spironolactone, bisoprolol and doxazosin (bisoprolol and doxazosin can be interchanged for any concomitant indication like benign enlargement of the prostate or palpitations).
Table 10: Drug treatment of hypertension with compelling indications

Numbers 1, 2, 3, 4, 5, 6 are given in order of priority of usage, 1 being first; *drugs can replace main line drugs; ^use where fluid clearance is required for fluid overload; # may be used if concomitant issues of arrhythmia; R is replacement therapy; S is special consideration; for Beta blockers other drugs like nebivolol, carvedilol, etoprolol, atenolol may be considered depending on the medications; replacement medication can also be used in cases of side effects of mainline therapy e.g., CCB-NDHP for beta blockers in asthma patients. The role of Lasix in HF/low EF may be variable; Carvedilol preferred in HTN with CHF. CVD includes coronary artery, and neurovascular diseases, e.g., MI, stroke etc. CKD^^ is divided into pre-dialysis and patients on HD. ** SGLT2 inhibitors delay progression of proteinuria in CKD and may be an add on therapy.

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.[15-17] Verdecchia et al's data[18] support prior observations that certain antihypertensive drug

classes (diuretics and β-blockers) may increase this propensity in patients with hypertension to develop type 2 diabetes.[17] 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.[19] The same has been noted in other trials for diuretics as compared to ACE, ARBs and CCBs inhibitors.[20, 21] 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.[22]

16.3 Combination Therapy (Free Versus Fixed Dose Single Pill Combination)

Initiating single pill 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 FDC.[23,24] Adherence to fixed-dose combination therapy of CCB with ACE inhibitors was significantly greater than for free combination therapy.[23] Patients receiving a once-daily, single-capsule, fi ed-dose combination of ACE and CCB demonstrated better medication adherence than subjects receiving ACE and CCB as separate components.[24] Initiating FDC therapy with diuretic and ACE inhibitors, ARB, or beta-adrenergic blocking agent was associated with better adherence as compared to diuretic monotherapy.[25] So it is recommended to try FDC as a primary form of therapy.

16.4 Scoring Fixed Dose Combination Pill

Do we get equal drugs, if we break an FDC single pill into half? This can be done for tablets that are scored by using appropriate pill cutters. Sustained release and coated tablets should not be halved. The Resolve to Save Lives Cardiovascular Health Initiative published a treatment protocol in partnership with the World Hypertension League, which features use of a single-pill FDC, as a first line choice in the management of hypertension[26] in their protocol, the single-pill FDC of choice is telmisartan 40 mg-amlodipine 5 mg, which they recommend be initiated as “half” of a tablet per day and titrated up to a maximum of two tablets. If two tablets are reached and BP is still uncontrolled, then it is recommended that a thiazide/thiazide-like diuretic be added. It is a simple approach, which could allow rapid titration and a corresponding quicker reduction in BP to goal, and is a viable approach for low- and medium-income countries. Many combination pills are not scored, but if guidelines stress the use of FDC, then scoring tablets will also become a tactical necessity for the industry.[27]

16.5 Resistant Hypertension [figure 4]

If the BP does not remain with in normal range even after use of maximum doses of three antihypertensive medicines, inclusive of 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 2nd line therapy for hypertension after the first line three drugs.

16.6 Refractory Hypertension [figure 4]

Refractory hypertension is defined as uncontrolled blood pressure despite use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and an MR (mineralocorticoid receptor) antagonist, at maximal or maximally tolerated doses[28] Patients with refractory hypertension typically exhibit increased sympathetic nervous system activity. Persistently higher heart rates, greater vascular stiff as indexed by pulse wave velocity, and greater 24-hour excretion of urinary norepinephrine is typical.[29] Therefore, use of sympatholytic agents should be beneficial, but use of effective doses of available agents that inhibit sympathetic output, such as clonidine, are attended by intolerable adverse effects. This is a highly refractory state and use of evolving, but still unproven device-based strategies, such as renal denervation or carotid sinus activation may be of value.[28] More randomized controlled trials are needed to address this issue.

16.7 Pseudo-Resistant Hypertension

The term "pseudo-resistance" refers to lack of BP control with appropriate treatment in a patient who does not have resistant hypertension. Several factors contribute to elevated BP readings and produce the perception of resistant hypertension.30-32 Such factors include the following:

- **i.** Suboptimal BP measurement technique
- **ii.** The white-coat effect
- **iii.** Poor adherence to prescribed therapy.[31, 33]

A pooled sample of 3,207,911 patients with hypertension on antihypertensive drugs (globally) were studied for

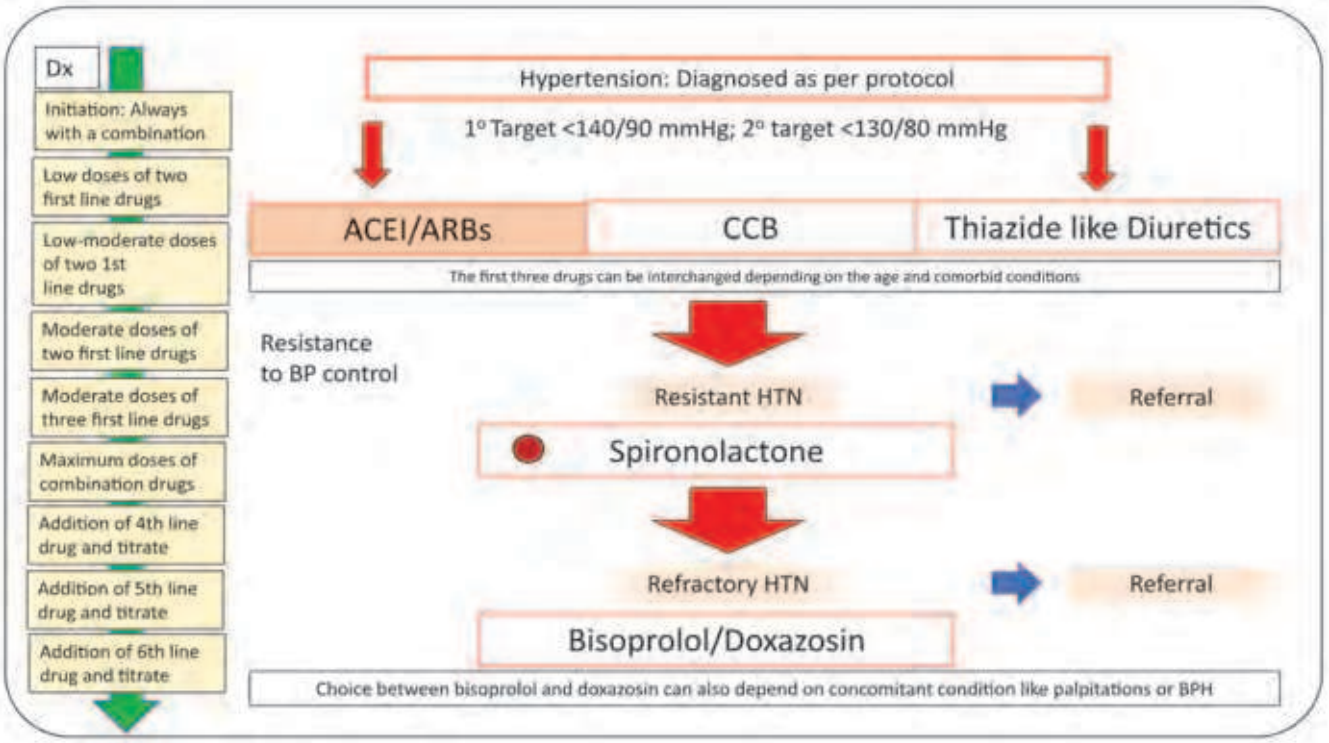

Figure-4: Drug Therapy: ACD-SDB approach.

resistant hypertension. In the general, population of treated patients with hypertension, the prevalence of true-resistant, apparent treatment-resistant and pseudo-resistant hypertension were 10.3% (95% CI 7.6% to 13.2%), 14.7% (95% CI 13.1% to 16.3%) and 10.3% (95% CI 6.0% to 15.5%).[34]

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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 with 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 mm Hg on at least three occasions, with normal ambulatory or home BP readings (24-hour ambulatory blood pressure <130/80 mm Hg or a home blood pressure reading of 135/85 mm Hg).[1] The failure to adequately diagnose WCH with standardized measurements has led to 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

hypertension mediated organ damage (HMOD), are associated with WCH.[6] In addition, over time, WCH can progress to sustained hypertension. Changing the typical protocol for office blood pressure measurement is recommended.[7] It is recommended to follow these patients closely for the development of HTN. Out of office or home BP is now recommended before initiation of drug therapy.[8] One tool that may be used to help identify those in need of confirmatory BP monitoring is the Predicting Out-of-Office BP (PROOF-BP) algorithm, which uses office BP measurements and clinical characteristics to predict a patient's out-of-office BP.[9]

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-office BP of ≥135/85 mm Hg.[10]

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.[11,12] It has been recommended that a positive diagnosis of masked hypertension be confirmed by ABPM before commencing antihypertensive therapy.[13,14]

Masked hypertension occurs 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 represents two 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.[15]

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18.0 Hypertension Crises [figure 5]

These include three of the following conditions:

18.1 Severe hypertension without hypertension mediated organ damage (HMOD)

When the BP is >180/120 mm Hg and there is no chronic HMOD, or ongoing acute target organ injury the condition is called severe hypertension.

18.2 Hypertensive Urgency

When the BP is >180/120 mm Hg and there is a chronic target organ damage without ongoing acute target organ injury, the condition is called hypertensive urgency. It does not require IV medications and only uptitration, needs 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.[1, 2]

18.3 Hypertensive Emergency

When the BP is >180/120 mm Hg and there is ongoing acute target organ injury or hypertension mediated organ damage (HMOD), the condition is called hypertensive emergency. It requires IV medications and the BP is brought down early but, in a protocol, directed and graded manner. Once discharged the follow-up is needed 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 HMOD is a major poor prognostic indicator. The main objectives of the management are distinction between emergency versus urgency and appropriate risk stratification, prevention or regression of acute HMOD 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 can be safely managed in the outpatient setting without exposing them to the risks of aggressive BP lowering. However, patients with HTN emergency requires hospitalisation, prompt treatment and close monitoring in the ICU setting.[3]

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

- Admit adults with a hypertensive emergency to an ICU for continuous monitoring of BP and HMOD, as

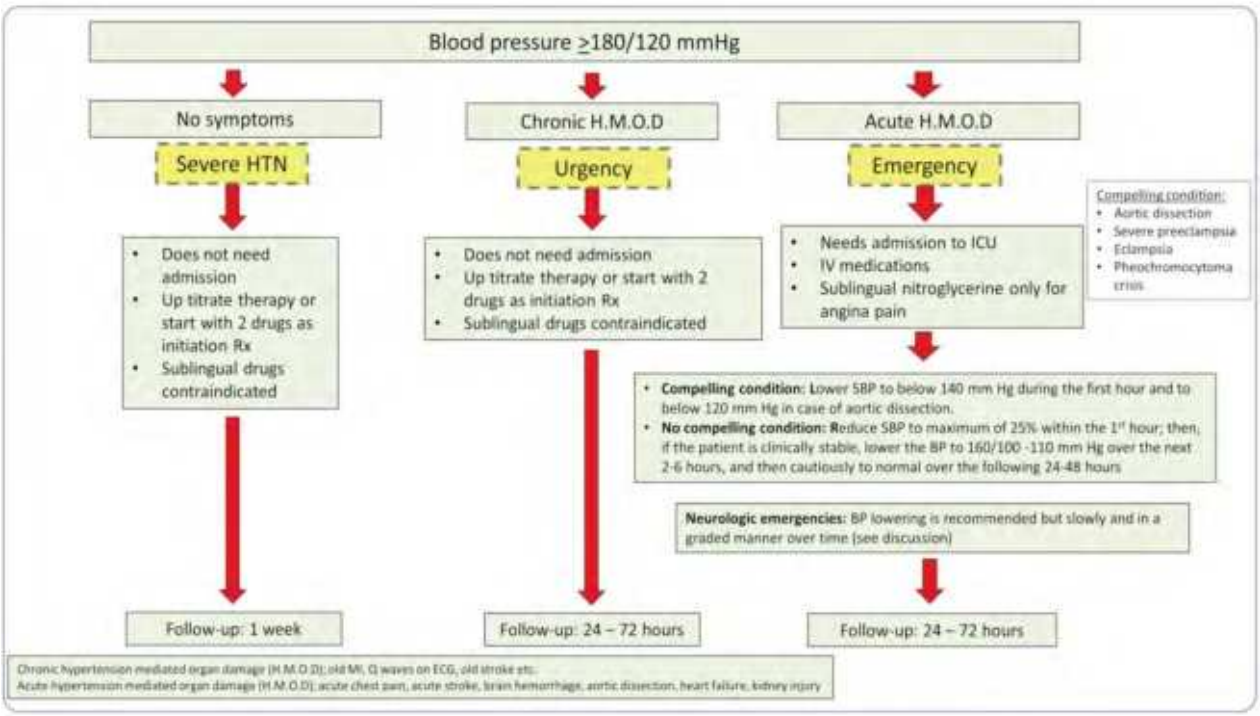

Figure-5: Management of hypertension crises.

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; if the patient is clinically stable, lower the BP to 160/100 -110 mm Hg over the next 2-6 hours, and then cautiously back to normal over the following 24-48 hours.[4]

18.3.1 Acute coronary syndrome

Beta-blockers and nitroglycerine (NTG) are the preferred drugs. NTG is 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 can be given 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 mm3, 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 nitro-glycerine/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. Beta-blockers can only be added after alpha blockade 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:

- o Hypertensive encephalopathy: Recommended to reduce the MAP 25% over 8 hours. Labetalol, nicardipine, esmolol are the preferred medications; nitroprusside and hydralazine should be avoided.
- o Acute ischaemic stroke: For acute ischaemic stroke immediate BP lowering is not recommended due to the Cushing effect that maintains cerebral perfusion in the acute phase. Therefore, hold antihypertensive medications:
- Unless the SBP is above 220 mm Hg or the DBP is over 120 mm Hg.
- 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]
- The preferred medications are labetalol and nicardipine.
- o Acute intracerebral haemorrhage: For acute intracerebral haemorrhage, the preferred medications are labetalol, nicardipine, and esmolol; avoid nitroprusside and hydralazine.
- 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]
- In adults with acute intracerebral haemorrhage 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 haemorrhage who present within 6 hours of the acute event and have an SBP between 150 and 220-mm Hg.[4]
- o Subarachnoid haemorrhage: The preferred drugs are nicardipine, labetalol, and esmolol; nitroprusside and

hydralazine should be avoided.

- Maintain the SBP below 160 mm Hg until the aneurysm is treated or cerebral vasospasm occurs. Although oral nimodipine is used to prevent delayed ischaemic neurologic deficits, it is NOT indicated for treating acute hypertension.[4]

18.4 Malignant Hypertension

Malignant hypertension is much less in the developed world, but it is still a problem in the low- and middle-income countries. The diagnosis is usually based on the association of severely elevated BP with a Keith and Wagener stage III or IV retinopathy. More recently, it has been suggested to consider that malignant hypertension with retinopathy is only one of several possible presentation(s) of acute hypertension with multiorgan damage (MOD). The presence of disturbance of at least three different target organs (kidney, heart, brain or microangiopathy) in association with acute BP elevation is described as 'hypertension MOD', which would need to be managed as a hypertensive emergency, even though retinopathy is lacking.[8]

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19.0 Pregnancy and hypertension[1]

Hypertension is the most common medical problem encountered during pregnancy, complicating up to 10% of pregnancies.[2]

Hypertension in pregnancy can be defined in four categories:

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

1. Preeclampsia:

Current definition of preeclampsia 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 oedema, or new-onset cerebral or visual disturbances [table 11, 12].

Table 11: Severe features of preeclampsia (any one of the features)

Variable	Features
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 Over 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 oedema	Pulmonary oedema
CNS/visual	New-onset cerebral or visual disturbances

Table-12: Risk factors for the development of preeclampsia

High risk features of preeclampsia
Hypertension in a previous pregnancy
Chronic kidney disease
Autoimmune disease e.g., SLE, or antiphospholipid syndrome
Type 1 or 2 diabetes
Chronic hypertension
Moderate risk features of preeclampsia
First pregnancy, age >40 years
Pregnancy interval of >10 years
BMI >35 kg/m2 at first visit
Family history of preeclampsia
Multiple pregnancy

Journal of Hypertension. 2013;31:1281-1357.

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

19.1 Diagnosis of HTN in pregnancy

BP readings of ≥140/90 mm Hg on two occasions 4 hours apart.

Thresholds for treatment include:

- BP ≥ 140/90 mm Hg and proteinuria
- BP ≥ 160/110 mm Hg 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 6, table 13a, 13b]

It is recommended to closely monitor women with gestational hypertension or preeclampsia without severe

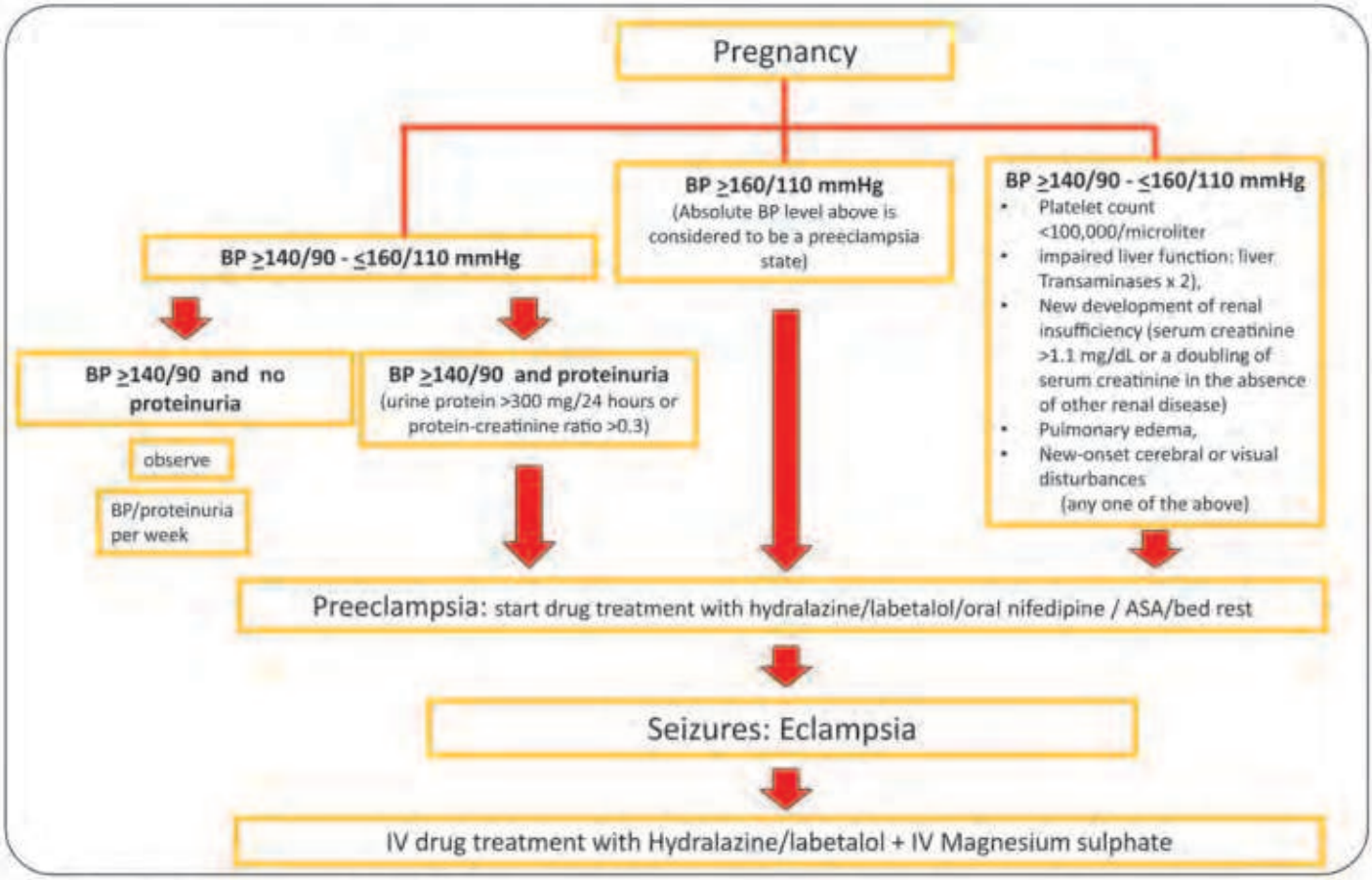

Figure-6: Algorithm for the management of hypertension in pregnancy.

Table-13a: Drug treatment in pregnancy – first line drugs

Drugs	Dose	FDA Class	Safety	Side Effect	Breast Feeding
Methyldopa	0.5 to 3 g/day in 2divided doses	B	Proven safety andefficacy	Some concern with depression, Hepatic disturbances, haemolytic anaemia, may not lower BP adequately	Compatible with breast milk
Labetalol	200 to 1200 mg/dayper oral in 2-3 divided doses 20-40 mg IV (max 220 mg total)	C	Safety similar tomethyldopa may be more efficientthan methyldopa	May be associated withfoetal growth restriction. Neonatal hypoglycaemia with larger doses	Usually, compatiblewith breast milk

Modified from Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. Drugs. 2014;74: 283-296.

Table 13b: Drug treatment in pregnancy - second line drugs

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	Usually compatible with breast milk
Verapamil	80 mg three times a day per oral	C	Similar efficacy to other oral Agents	Risk of interaction with magnesium - bradycardia	Usually compatible with breast milk
Clonidine Alternative option	0.1- 0.6 mg/day in 2 divided doses	C	Safety similar to methyldopa	Efficacy similar to methyldopa	Possible breast milk effects
Hydrochlorothiazide Useful in chronic hypertension	12.5- 25 mg/day	B	Limited data regarding foetal safety	Volume contraction, electrolyte abnormalities-rare with small dose	May reduce breast milk production
Hydralazine(Not recommended by ESH)	50-300 mg/d in 2-4 divided doses	D	Efficacious IV agent	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;74: 283-296.

features, with serial assessment of maternal symptoms and foetal 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.

19.3 Anti-hypertensive Drugs to Treat Severe Hypertension in Pregnancy

The objectives of treating severe hypertension are to prevent potential cardiovascular (congestive heart failure and myocardial ischaemia), renal (renal injury or failure), or cerebrovascular (ischaemic or haemorrhagic stroke) complications related to uncontrolled severe hypertension [table 13a and 13b]. No randomized trials in pregnancy are identified to determine the level of hypertension for treating its 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, revealed increased rates of heart failure, pulmonary oedema, 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 anti-hypertensive 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] Available evidence suggests that oral nifedipine also may be considered as a first -line therapy.[3] When urgent treatment is needed before the establishment of IV access, the oral nifedipine algorithm can be initiated as IV access is being obtained, or a 200-mg dose of labetalol can be administered orally. The latter can be repeated in 30 minutes if appropriate improvement is not observed.[3]

Theoretical concern exists that the combined use of nifedipine and magnesium sulphate 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.[4] Magnesium sulphate is not recommended as an antihypertensive agent, but magnesium sulphate remains the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia.[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.[5] If a woman's BP is well controlled on an agent pre-pregnancy, she may continue it during pregnancy, with the exception of ACE inhibitors & 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.[5] It is also recommended that methyldopa and labetalol are appropriate first-line agents and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended.[6,7]

19.3.3 Magnesium Sulphate:

In a Cochrane review of treatment of women with preeclampsia, magnesium sulphate more than halved the risk of eclampsia, and probably reduced maternal death.[8]

19.3.4 Aspirin Use:

Doses up to 75 mg appear to be safe. Women at high risk of preeclampsia or with more than one moderate risk factor for preeclampsia may be advised to take 75 mg of aspirin daily from 12 weeks until the birth of the baby, provided that they are at low risk of gastrointestinal haemorrhage.[9]

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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 mm Hg.[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] 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

Traditionally the octogenarian (80 years or above) population has been overlooked and excluded in studies in the past, but recent data demonstrate CVD benefits in treating HTN in older adults. This comes from several key studies, including the UK Prospective Diabetes Study (UKPDS),[8] the Systolic HTN in the Elderly Program (SHEP),[9] SPRINT,[10] the Systolic HTN in Europe trial (Syst-Eur),[11] Medical Research Council Working Party[12] and the HTN in the Very Elderly Trial (HYVET).[13] Thus, recognition and appropriate treatment of HTN in older adults should be a priority for physicians.

Principles of Initiation of Therapy Include:

i. Lower initial doses (approximately one-half of that in the younger patient) should be used to minimize the risk of side effects.

ii. 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, BP 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 ischaemic symptoms, particularly in patients with orthostatic hypotension. This approach is consistent with recommendations made by the European Society of Hypertension/European Society of Cardiology.[14]

iii. 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)10 included a large number of hypertensive older adults (aged 75 years or older) who were less fit or frail at the time of enrolment. As noted below, the benefit 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 BP.

iv. When treating older adults and especially frail older adult hypertensive patients, 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 is/are found in as many as 20 percent of the older adult patients with isolated systolic hypertension.[15,16] Hypertensive older adults with orthostatic hypotension are significantly more likely to fall than those without orthostatic hypotension.[17,18] 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.[19]

As a result, supine and standing pressures should be measured in older adult patients prior to the initiation of antihypertensive therapy (whether BP is 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 mm Hg fall in systolic blood pressure
2. At least a 10 mm Hg 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 verifified by timely measurement of BP.

20.5 Problem of frailty

With the exception of SPRINT[10], 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 fitness.

- In a cohort of 1,127 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 of less than 130 mm Hg

(32%).20 In comparison, mortality was lower among individuals who had higher blood pressure despite taking two or more antihypertensive drugs (20%) and among those taking fewer medications, who had systolic BP above and below 130 mm Hg (20 & 18%, respectively). The adjusted hazard ratio for death was greater for those who had a systolic BP < 130 mm Hg 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%, and 35 versus 18%, respectively).

- In an observational study of 2340 adults older than 65 years, the association between BP and mortality was examined whether or not individuals were frail (deficiency as an inability to walk 6 meters in less than 8 seconds)21. According to the study, the frail adults had no association between BP and mortality. In addition, a higher BP was reported to be associated with a lower risk of death among the most frail (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 trial10 found a similar benefit from more as compared with less intensive BP 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.

The multiple trial data presented above supports the following recommendations.

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 intervention (NPI), 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 monotherapy with:
a. Low-dose thiazide-like diuretic, a long-acting CCB, or an ACE inhibitor/ARB
b. In patients with a reasonable likelihood of requiring a second drug (e.g., systolic pressure more than 10/5 mm Hg 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

The goal is to attain a systolic pressure of 125 to 135 mm Hg (office BP) measurements. If goal BP 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 the clinic for history with vital signs check and postural BP assessment. Unless there is a "safety net" of family physicians/general practitioners follow-up, this tight control should not be pursued. Home BP monitoring is an essential tool in the management of BP in the elderly. The patient or attendant should be trained to measure the BP as per protocol and keep a record. They should be educated at each visit regarding signs of low BP.

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21.0 Hypertension in the paediatric population

Hypertension, including essential, or primary, hypertension, is not limited to adults, but is also detectible in childhood.[1] Owing to several factors such as the ongoing nutritional transition, increasing trends in sedentary lifestyle and other modifiable risk factors, and inadequate health care systems, populations in low-and middle-income countries (LMICs) may bear a higher burden of the disease, compared with the global average.[2]

The origins of hypertension in adulthood extend to childhood ages, Barker in 1986 linked adult-onset cardiovascular disease to prenatal nutrition.[3] The frequency of increased BP in adolescence progresses to hypertension by 7% yearly.[4] In the light of these data, new studies related to childhood hypertension have been conducted, and globally hypertension guidelines have been updated in view of the information obtained.

There are mainly two guidelines for childhood hypertension.

- The American Academy of Paediatrics (AAP) and its Council on Quality Improvement and Patient Safety developed a practice guideline to provide an update on topics relevant to the diagnosis, evaluation, and management of paediatric HTN in the outpatient services. These guidelines are endorsed by the American Heart Association (AHA).[5]
- The European Society of Hypertension (ESH) guideline, which was constituted and published by the ESH in 2009 and updated in 2016.[6]

21.1 Definition [table 14]

A BP value below the 90th percentile by age, sex, and height is considered as normal. Normative BP tables include SBP and DBP values arranged by age, sex, and height (and height percentile). In view of paucity of local data and scant literature internationally, PHL has endorsed the recommendations of the above two guidelines.

Simplified BP Table [table 15]

Based on the 90th percentile for age, and sex for children at the 5th percentile of height has been introduced for initial outpatient screening of children. This table is recommended for screening tool to identify children who need further BP evaluation, it should not be used to diagnose HTN by itself.[5]

Table-14: Updated Definition of BP Categories and Stages according to AAP

For Children Aged 1–<13 y	For Children Aged ≥13 y
Normal BP: <90th percentile	Normal BP: <90th ercentile
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg

Table-15: Screening BP Values Requiring Further Evaluation

Age	BP, mm Hg			
	Boys		Girls	
	SBP	DBP	SBP	DBP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

21.2 Cuff size

The correct cuff size should be used. The bladder length should be 80%–100% of the circumference of the arm, and the width should be at least 40%.

21.3 Primary and Secondary Causes of Hypertension

The correct cuff size should be used. The bladder length should be 80%–100% of the circumference of the arm, and the width should be at least 40%.

- Children with primary hypertension are usually older (≥6 years), positive family history (in a parent and/or grandparent) of HTN, and overweight and/or obesity. BP elevation severity has not differed significantly between children with primary and secondary HTN but Diastolic BP elevation appears to be more predictive of secondary HTN, whereas systolic HTN appears to be more predictive of primary HTN.[7]
- Renal disease and Reno vascular disease are among the most common secondary causes of HTN in children.
- Coarctation of the aorta (COA) is a congenital abnormality of the aortic arch characterized by discrete narrowing of the aortic arch, generally at the level of the aortic isthmus. It is usually associated with HTN and right arm BP that is 20 mmHg (or more) greater than the lower extremity BP, children with abdominal aortic obstruction may have neurofibromatosis, Williams syndrome, Alagille syndrome, or Takayasu arteritis. Children with COA can remain hypertensive after successful repair/intervention. Their office blood pressures also might be normal; these children require Ambulatory blood pressure monitoring to diagnose masked hypertension (MH). This is a strong recommendation from AAP.[8]
- HTN resulting from hormonal excess accounts for a relatively small proportion of children with secondary HTN.
- Neurofibromatosis type 1 (NF-1) (also known as Von Recklinghausen disease) is a rare autosomal dominant disorder have secondary HTN due to renal artery stenosis.
- Many over-the-counter drugs, prescription medications, alternative therapies (i.e., herbal and nutritional supplements), dietary products, and recreational drugs can increase BP including oral contraceptives, central nervous system stimulants, and corticosteroids.

21.4 Management of hypertension in the paediatric population

21.4.A Normal BP

No additional action is needed. Practitioners should measure the BP at the next routine well-child care visit.

21.4.B Elevated BP

- Lifestyle interventions should be recommended (i.e., healthy diet, sleep, and physical activity).
- The measurement should be repeated in 6 months by auscultation.
- Nutrition and/or weight management referral should be considered as appropriate.
- If BP remains at the elevated BP level after 6 months,

upper and lower extremity BP should be checked, lifestyle counselling should be repeated, and BP should be rechecked in 6 months (i.e., at the next well-child care visit) by auscultation.
- If BP continues at the elevated BP level after 12 months (e.g., after 3 auscultatory measurements), Ambulatory blood pressure (ABP) should be ordered (if available), and diagnostic evaluation should be conducted.
- If BP normalizes at any point, return to annual BP screening at well-child care visits.

21.4.C Stage 1 HTN
- In the asymptomatic patient, provide lifestyle counselling and recheck the BP in 1 to 2 weeks by auscultation.
- If the BP reading is still at the stage 1 level, upper and lower extremity BP should be checked and BP should be rechecked in 3 months by auscultation.
- If BP continues to be at the stage 1 HTN level after 3 visits, ABPM should be ordered (if available), diagnostic evaluation should be conducted, and treatment should be initiated. Subspecialty referral should be considered.

21.4.D Stage 2 HTN
- Upper and lower extremity BP should be checked, lifestyle recommendations given, and the BP measurement should be repeated within 1 week. Alternatively, the patient could be referred to subspecialty care within 1 week.
- If the BP reading is still at the stage 2 HTN level when repeated, then diagnostic evaluation, including ABPM, should be conducted and treatment should be initiated, or the patient should be referred to subspecialty care within 1 week.
- If the BP reading is at the stage 2 HTN level and the patient is symptomatic, or the BP is >30 mm Hg above the 95th percentile (or >180/120 mm Hg in an adolescent), refer to an immediate source of care, such as an emergency department (ED).

21.5 Treatment

21.5. A Lifestyle and Non-Pharmacologic Interventions

The Dietary Approaches to Stop Hypertension (DASH) approach and specific elements of that diet have been the primary dietary strategy tested in the literature. These elements include a diet that is high in fruits, vegetables, low-fat milk products, whole grains, poultry, nuts, and lean red meats; it also includes a limited intake of sugar and sweets along with lower sodium intake.

Vigorous physical activity at least 3 to 5 days per week (30–60 minutes per session) to help reduce BP.

21.5. B Pharmacologic Treatment

Children who remain hypertensive despite a trial of lifestyle modifications or who have symptomatic HTN, stage 2 HTN without a clearly modifiable factor (e.g.,

Summary of screening and management

BP Category	BP Screening	Lifestyle counselling	Complete physical examination with upper and lower limb BP	ABP	Diagnostic evaluation (UCE, ECHO, Renal ultrasound)	Initiate treatment	Consider sub specialityconsult
Normal	Annual	Yes	-	-	-	-	-
Elevated BP	Initial BP	Yes	-	-	-	-	-
	Repeat BP after 6 months	Yes	Yes				
	Repeat BP after 6 months	Yes		Yes	Yes	-	-
Stage 1 HTN	Initial BP	Yes	-	-	-	-	-
	Repeat BP in 1-2 weeks	Yes	Yes				
	Repeat BP in 3 months	Yes		Yes	Yes	Yes	Yes
Stage 2 HTN	Initial BP	Yes	Yes	-	-		
	Repeat with sub specialty in 1 week	Yes	Yes	Yes	Yes	Yes	Yes

obesity), or any stage of HTN associated with CKD or diabetes mellitus therapy should be initiated with a single medication at the low end of the dosing range.

- If BP is not controlled with a single agent, a second agent can be added to the regimen and titrated as with the initial drug.
- Pharmacologic treatment of HTN in children and adolescents should be initiated with an ACE inhibitor, ARB, long-acting calcium channel blocker, or a thiazide diuretic.
- In view of the expanded adverse effect profile and lack of association in adults with improved outcomes compared with other agents, β-blockers are not recommended as initial treatment in children.
- In children with HTN and CKD, proteinuria, or diabetes mellitus, an ACE inhibitors or ARBs are recommended as the initial antihypertensive agent unless there is an absolute contraindication.
- In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic HTN, or stage 2 HTN without a clearly modifiable factor [e.g., obesity]), clinicians should initiate pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic diabetes mellitus therapy should be initiated with a single medication at the low end of the dosing range.

21.5.C Follow-up and Monitoring

- If pharmacotherapy is started, patient should be seen every 4–6 weeks for dose adjustments and/or addition of a second or third agent until goal BP has been achieved. After that, the frequency of visits can be extended to every 3 to 4 months.
- If only lifestyle changes are advised, then follow-up visits can take place every 3–6 months so that adherence to lifestyle change can be reinforced and the need for initiation of medication can be reassessed.
- In patients treated with antihypertensive medications, home BP measurement is frequently used to get a better assessment of BP control.
- Repeat ABPM may also be used to assess BP control and is especially important in patients with CKD.

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22.0 Secondary Hypertension

This requires a referral to a specialist who deals with hypertension. About 10% of patients with hypertension have a secondary cause. Clinicians often consider

Table 16: Causes, signs and symptoms and investigations for secondary hypertension

Diseases	Signs and Symptoms	Investigations
Renal Artery Stenosis	Renal bruit	Ultrasonography
Renal Parenchymal Disease	Mostly Asymptomatic	Serum creatinine test
Primary Aldosteronism	Mostly Asymptomatic	Aldosterone and renin level
Pheochromocytoma	Episodic headache	24-hour urinary fraction
Cushing Syndrome	Moon facies	24-hour urinary cortisol
Hypothyroidism	Symptom of hyperthyroidism	Thyroid function test
Coarctation of the aorta	Radio femoral delay	Transthoracic echocardiogram
Obstructive Sleep Apnoea	Obesity	Polysomnography
Medications	Oral contraceptive	NA

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 apnoea (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]

Table 16 demonstrates the signs and symptoms and recommended tests. This condition requires referral to a specialist, who specializes in the management of secondary hypertension, as managing the underlying condition may help cure the hypertension.

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23.0 Drug treatment of hypertension with compelling indications

Treatment starts with non-pharmacologic intervention and then the ACD-SDB algorithm is used for HTN without compelling indication. The guideline takes departure from the main algorithm when compelling indications are present. This variation in approach is based on the principle of starting evidence-based drugs that provide morbidity and mortality benefit, if used earlier on in the course. Example is a hypertensive patient who has a high-risk condition (e.g., heart failure, recent myocardial infarction, diabetes, chronic kidney disease) that constitutes a compelling indication, and mandates the use of a non-first line antihypertensive drug class. In the case that initial treatment should be dictated by the compelling indication, BP control is paramount.[1] The compelling indications are diabetes mellitus, CV disease (included coronary disease and stroke), CKD with and without proteinuria, and heart failure (clinical heart failure or low EF without symptoms).

23.1 Diabetes Mellitus (DM)

Approximately 74% of patients with type 2 DM have HTN. The San Antonio Heart Study showed that 85% of the trial participants had HTN by the 5th decade of life.[2] A cluster of atherogenic changes may precede the development of hypertension and increased fasting insulin concentration predicts hypertension in important subgroups of subjects. Therefore, it is important to choose the right drugs for the initiation of therapy. PHL maintains the BP target for DM patients as primary target of 140/90mm Hg and if tolerated a secondary target of 130/80 mm Hg. The BENEDICT, ROADMAP, IRMA[2], IDNT, RENAAL and Captopril trials[3-8] showed benefit in achieving end points compared with placebo and in the BENEDICT trial also with verapamil. The ACE inhibitor trandolapril showed a renal protective effect through reducing microalbuminuria. In the ROADMAP trial, the investigators concluded that RAS blockade with Olmesartan might cause sustained reduction (legacy effect) of micro- and macrovascular events.[4] IRMA 2 trial showed that among hypertensive patients with type 2 DM and persistent microalbuminuria, treatment with irbesartan significantly reduced the rate of progression to clinical albuminuria.[5] The IDNT trial showed that the ARB irbesartan demonstrated a significantly decreased incidence of endpoints assessing the progression of renal disease compared to amlodipine and to placebo. These effects appeared to be independent of irbesartan's effects in lowering BP.[6] In the RENAAL trial Losartan conferred significant renal benefit in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.[7] In the Captopril trial, in DM patients' captopril protected against deterioration in renal function in insulin-dependent diabetic nephropathy and was significantly more effective than BP control alone.[8]

When ACE inhibitor is added to either a CCB or a diuretic, both combinations significantly reduced BP and urinary albumin to creatinine ratio ($P < 0.0001$ for all); however, the median reduction in urinary albumin to creatinine ratio achieved with a benazepril–diuretic combination was significantly greater than that obtained with a benazepril–CCB combination (−72.1% vs −40.5%; $P < 0.0001$). Furthermore, the percentage of patients with

microalbuminuria who attained a normal urinary albumin to creatinine ratio was higher with combined ACE inhibitors–diuretic therapy than with combined ACEI–CCB treatment (69.2% vs 47.8%; P = 0.0004). Conversely, the mean reduction in diastolic BP was significantly greater in the ACE inhibitor–CCB group than in the ACE inhibitor–diuretic group (–13.1 mm Hg vs –9.97 mm Hg; P = 0.02). Both combinations were well tolerated.[9] The PATHWAY 2 trial paved the way for spironolactone to come in as a treatment for resistant HTN. The trial had 14% diabetic patients. Spironolactone is highly effective in lowering blood pressure in patients with type 2 diabetes and poorly controlled hypertension on standard treatment.[10]

PHL recommends:
ARB/ACE inhibitor, DHP-CCB, Thiazide like or type diuretic (depending on the availability), spironolactone, doxazosin, bisoprolol, hydralazine. When BP is not controlled after 3 drugs at maximum doses a referral should be sought. Subsequently, at a stage where 5 drugs at maximum doses (ensure compliance) have not controlled BP referral is strongly recommended.

23.2 Chronic kidney disease

Treatment of HTN is vital in the management of CKD, including patients with end stage renal disease (ESRD). HTN is both a cause and a consequence of CKD, and its prevalence is high among patients with CKD and ESRD.[11,12] Patients with CKD have an outsized burden of cardiovascular disease; indeed, the presence of CKD represents a coronary risk equivalent on par with diabetes mellitus.[13] Treatment is associated with improved CV outcomes in both CKD14 and ESRD.[15] Thus, the management of hypertension in CKD and ESRD is an important and urgent issue. Based on evidence, for predialysis CKD and in the absence of specific indications for other drugs, prescribe an ACEi or ARB as first -line therapy for hypertension patients with CKD stage >3, or with albuminuria of at least 300 mg/d or 300 mg/g creatinine on spot check. The second-line choice is between a DHP-CCB or a diuretic (if volume overload). In patients with resistant hypertension, spironolactone is added based on the PATHWAY 2 trial. Importantly, this is an extrapolation to the CKD population, because the PATHWAY-2 Trial excluded subjects with CKD stage 3B or worse, and the average eGFR was 91 ml/min per 1.73 m^2 for trial subjects.[16] For patients on haemodialysis (HD), the HDPAL study showed that among maintenance HD patients with HTN and LVH, atenolol-based antihypertensive therapy may be superior to lisinopril-based therapy in preventing cardiovascular morbidity and all-cause hospitalizations.[17] Atenolol as first drug, CCB (NDHP-CCB if proteinuria), ACE inhibitor/ARB, spironolactone (make sure potassium is treated before initiation).[17] Peripherally acting alpha blockers (alpha adrenoceptor antagonists; such as doxazosin) are commonly used as part of combination therapy for the management of hypertension in CKD. This may be due to a pharmacokinetic profile that is undisturbed by declining eGFR in addition to favourable effects on glycaemic control.[18] The non-dihydropyridine calcium channel blockers (NDHP), diltiazem and verapamil, slow the progression of type 2 diabetic nephropathy with overt proteinuria almost to a similar extent as observed with ACE inhibitors.[19]

PHL recommends:
Pre-dialysis CKD: ARB/ACE inhibitor, DHP-CCB, Thiazide like or type diuretic (depending on the availability), spironolactone, doxazosin, bisoprolol, hydralazine.

When BP is not controlled after 3 drugs at maximum doses a referral should be sought. Subsequently, at a stage where 5 drugs at maximum doses (ensure compliance) have not controlled BP referral is strongly recommended.

Haemodialysis (HD): Atenolol as first drug, CCB (NDHP-CCB if proteinuria), ACE inhibitor/ARB, spironolactone (make sure potassium is treated before initiation).

23.3 Ischaemic Heart Disease

Meta-analyses of antihypertensive trials have demonstrated that BP lowering is more important than the particular drug class used in the primary prevention of the complications of hypertension, including IHD. However, for secondary protection in individuals with underlying comorbid illnesses such as IHD, CKD, or recurrent stroke, not all drug classes have been proven to confer optimal or even the same level of benefit .[20]

Thiazide and thiazide-like diuretics chlorthalidone and indapamide are highly effective in reducing BP and preventing cerebrovascular events, as seen in the Veterans Administration studies[21], the Medical Research Council (MRC) Trial[22], the Systolic Hypertension in the Elderly Programme (SHEP)[23], and the Hypertension in the Very Elderly Trial (HYVET).[24] The benefit of chlorthalidone-based therapy in hypertension treatment is evident from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[25]

Beta Blockers remain the standard of care in patients with

angina pectoris, post MI and LV dysfunction with or without symptoms of HF, unless contraindicated. Carvedilol, metoprolol and bisoprolol have been shown to improve outcomes in patients with HF.[26] Nebivolol has unique pharmacological profile and clinical evidence supports its utility in the treatment of HTN with both CV (HF with reduced EF, CAD & AF) and non-CV comorbidities (DM, COPD, erectile dysfunction [ED]).[27] However, the largest limitation in interpreting nebivolol trial data comes from the absence of long-term outcome trials, as well as direct comparative trials data assessing its effect on CV morbidity and mortality versus other beta blockers.[28]

ACE inhibitors are effective in reducing initial IHD events and are recommended for consideration in all patients after MI. They are proven to prevent and improve both HF.[29,30] When combined with thiazide diuretics, ACE inhibitors reduce the incidence of recurrent stroke.[31]

PHL recommends

For stable ischaemic heart disease, the recommendation is to start with ACE inhibitors/ARBs, beta blockers, DHP-CCB, thiazide like diuretics, spironolactone, doxazosin. Referral is warranted if BP is uncontrolled with maximum doses of three first line drugs. Subsequently, referral is recommended if BP remains uncontrolled on maximum doses of 5 drugs.

J curve: The J-curve phenomenon was first observed in connection with myocardial infarction for diastolic BP in treated hypertension32. Although there is very little clinical trial evidence of the J-curve issue, there is abundant observational evidence indicating a nadir level of BP below which BP lowering might be detrimental.33 More randomized controlled data to establish an evidence base is needed to settle this myth.

23.4 Congestive heart failure (CHF) and asymptomatic low EF

Patients with CHF and EF less than 45% have shown clinical benefit with primary endpoint achievement in the PARADIGM HF trial.[34] Sacubitril valsartan was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. In the trial 70% patients had HTN in both the arms. The PARAMETER study (Prospective Comparison of Angiotensin Receptor Neurolysin Inhibitor With Angiotensin Receptor Blocker Measuring Arterial Stiff in the Elderly), for the first time, demonstrated superiority of sacubitril/valsartan versus Olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in elderly patients with systolic hypertension and stiff arteries.[35] In the Asian landscape a total of 14 sacubitril/valsartan trials achieved great results for different grades of hypertension, including: grade 1 and 2 hypertension, refractory hypertension, hypertension in the elderly, salt-induced hypertension among others.[36, 37] The three drugs, that is ACE inhibitor, ARB and ARNI should not be used simultaneously. An ARNI should not be used with an ACEI (wait at with[36] hours when switching to or from ACE inhibitor to avoid hypotension, hyperkalaemia and/or life-threatening angioedema). Avoid use of an ARNI with an ARB. Avoid use of an ARB with an ACEI, as there is limited evidence of benefit from combined use of these drugs in this setting.[38]

Beta blockers, ACE inhibitor, ARBs, ARNIs, mineralocorticoid receptor antagonist (MRA), have become the standard of care for heart failure patients.[39]

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24.0 Follow-up

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 BP control. 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 have been noted with hypertension emergencies and have been 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 borderline elevated BP only, the suggested follow-up is after 1 year. At which point assessment of healthy lifestyle changes, target weight achievement and exercise routines should be looked at. For severely elevated BP, bringing the BP down is discouraged now, as a sharp decrease in BP may lead to hypoperfusion and loss of consciousness, ischaemic stroke, and myocardial infarction.

25.0 Special concerns

25.1 Use of sublingual drugs to lower BP acutely

It has been a practice, highlighted in various studies that sublingual drugs like nifedipine and captopril can be used to bring down severely elevated BP. For both severe HTN (BP >180/120 mm Hg) and no symptoms with or without chronic HMOD, the use of sublingual drugs is contraindicated. Although used in the past, sublingual nifedipine is no longer recommended due to its propensity to cause severe hypotension and organ ischaemia[1], which may lead to loss of consciousness, ischaemic stroke, and myocardial infarction.[2]

25.2 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] Therefore, benzodiazepines may only be used in HTN patients, if the patient has been diagnosed with established anxiety neurosis using objective assessment by an expert. Benzodiazepines or other anxiolytics are not first line antihypertensive therapy and should not be used.

The use of benzodiazepines for chronic treatment of arterial hypertension is not recommended.[5] A study of clinical practice patterns of benzodiazepine use, showed that 21% of patients took benzodiazepines for hypertension treatment.[6] The use of benzodiazepines in Pakistan (largely because of over-the-counter availability) has been observed to be higher than other developing countries, with only a small fraction of patients consulting a psychiatrist for the same.[7]

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26.0 Summary

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 at the population level. The strategy addresses BP ranges that were considered normal in the past. We know that SBP above 115 mm Hg carries a risk, and tight control of BP to around or less than SBP 120 mm Hg, carries benefit with acceptable level of adverse effects with strong recommendation for non-pharmacological management strategy. Therefore, the PHL guidelines now define the non-pharmacologic intervention in steps 0, 1 and 2. Step 0 is creating awareness and educating the population, who do not yet have high BP. This is in keeping with the home health education (HHE) that was prescribed in the COBRA trial and yielded significant benefit to create an awareness level. Step 0 is a tool rather than just an idea. Followed by Step 1 that includes a recommendation with a plan. However, Step 2 is more than just a home-based plan and includes a supervised programme for exercise, diet and smoking cessation. This is yet not developed in Pakistan but is the need of the day. It is recommended that such facilities be provided to the population in a pragmatic and logistically feasible way.

Drug therapy includes the ACD as first line drugs (the distinction of order of priority in the first three drugs has been removed) and spironolactone as the 2nd line therapy (or the 4th drug to be introduced). Additionally, doxazosin and bisoprolol are the 5th and 6th line therapy. ACE inhibitors are now considered equal to ARBs in the management of hypertension. ARBs come with a relatively better safety profile. It remains at the discretion of the physician, to choose the RAAS inhibitor/blocker that best suit the patients. Sustained availability at affordable price, availability in combinations and side effect profile, all lend to the priority in choosing. For diuretics the longer ones are preferred over HCTZ that is chlorthalidone and indapamide. However, HCTZ is cheap and most often used diuretic in combination. Therefore, when combinations are being used, it is imperative that the longest acting agents are chosen in combination with the shorter acting HCTZ.

Combination therapy is now being recommended for all patients. Single drug therapy for initiation is only recommended for the very frail/elderly. The rest of the groups start therapy with a small to moderate dose of two first line antihypertensive drugs. The starting point BP value is the discriminator for the choice of combination dose. For lower range hypertensive values, small doses of two first line drugs are recommended. This is after the nonpharmacologic intervention has been given time. Small doses of first line drug combinations like amlodipine/telmisartan are not available; only moderate doses like amlodipine/telmisartan (5/40) are present. Scoring such combination pills is being considered, although presently, most do not have a scoring line, which does not ensure equal distribution of doses. Internationally, it is a need that is being realized, and in the future, one can expect the industry to provide combination pills with proper evidence-based scoring recommendations. This will provide a greater choice for use of combination therapy, will help in better control and will possibly cut the cost (most needed for LMICs).

Special populations like HTN in pregnancy, the elderly, with compelling indications and the paediatric population are also discussed. Similarly, HTN crises are defined with clear distinctions made between severe HTN, HTN urgencies and emergencies. Lastly, the issue of anxiolytics being wrongly used as first line anti HTN therapy has also been highlighted, use of sublingual drugs (other than angised for angina) is discussed for lowering severe HTN and strongly discouraged.

The PHL 2022 guideline in keeping with the previous version includes case vignettes. There are 24 case vignettes that highlight most tactical points of the guidelines. These cases are presented as a workshop, which is an operational tool of the guideline document. An effort has been made to use algorithms, tables and figures to present scientific data, in a reader friendly format. The committee strongly feels that with approximately 26% adolescents and 46% adults having HTN, the problem is massive, and requires our immediate attention at the national as well as community level. All strategic efforts in the world that have shown to bring BP under good control that is 70% in the public and 90% in the private networks in the US, have shown commitment as the corner stone and they have used guidelines to achieve their goals.

27.0 Case Vignettes

Continuing the legacy of the past version of PHL national hypertension guidelines, the guideline committee is happy to include 24 case vignettes in this document for sound understanding of the real-life clinical scenarios and how to manage them. This will further the guidelines as an active reference document.

Case 01	
About patient	37 years old woman, active, careful about diet, BMI 23 kg/m2, BP: 130/80 mm Hg (averaged out on multiple clinic visits), strong family history of HTN (mother diagnosed at 35 years).
Question	She is concerned about her BP and wants to measure it at home. She wants to know about the best device recommendation for home BP monitoring.
Response	Mercury BP apparatus was the gold standard but it is toxic and therefore banned for use now. Mercury apparatuses are also cumbersome to use at home. They are well validated but require regular calibration and need skills to measure BP.Aneroid BP apparatus are easy to use but need calibration and are not validated and can break easily. Digital oscillometric BP apparatuses with upper arm (brachial cuff) are now the gold standard and are validated. They are extensively studied in large research studies.The wrist digital oscillometric apparatuses although easy to use are at risk of false readings due to arm position and are not well validated.

Case 02	
About patient	40 years old man, BMI 29 kg/m2, sedentary, BP checked on multiple occasions; twice at friend's home during lunch time (145/90 mm Hg), once at a health mela (150/90 mm Hg), twice at the shopping mall's health kiosk (145/90 mm Hg).
Question	Is he hypertensive?
Response	The patient may be hypertensive but BP readings are not taken in a standard fashion according to the prescribed protocol. Up to 15-30% patients can have white coat hypertension (WCH). The data set we are looking at suggest that SBP was on an average 30 mm Hg higher than normal. Therefore, to label someone hypertensive one must follow a guideline protocol. BP must be taken in a sitting position after 5 minutes of rest and after 30 minutes of food consumption. Feet on the floor, legs uncrossed, back supported and arms rested. Apply brachial cuff (appropriate size) with arterial marker over the brachial artery. Take the first reading and wait for one minute then take the second reading and average the two readings.

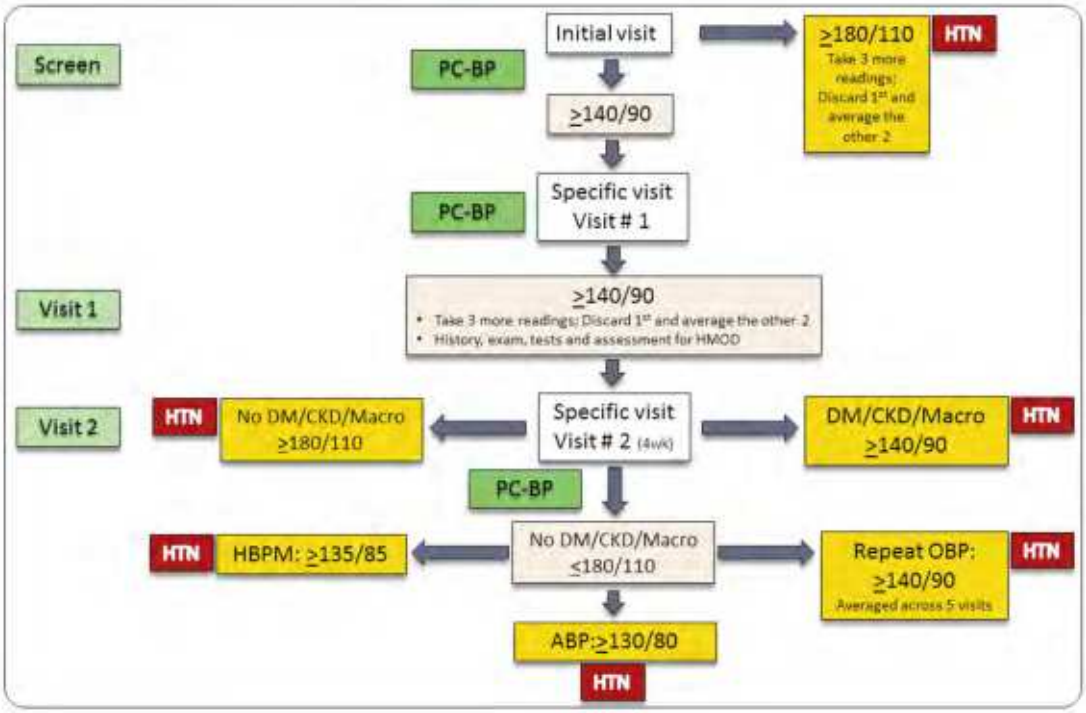

Figure-1: Diagnosis of Hypertension

PC-BP: post clinic BP, HMOD: hypertension mediated organ damage, OBP: office BP, HBPM: Home BP monitoring, ABP: Ambulatory BP monitoring, Macro: macro-vascular disease

Case 03	
About patient	40 years old man, BMI 29 kg/m2, sedentary, BP at home: average of 2 readings 1 minute apart at a specified time pre-breakfast and pre-dinner was 139/87 mm Hg for consecutive 4 days.
Question	Is he hypertensive? What is the target for home blood pressure monitoring (HBPM)? What is the advantage of HBPM, if any?
Response	Yes, he is hypertensive as his averaged reading over 4 days was 139/87 mm Hg. The HBPM target is <135/85 mm Hg. Above this level hypertension mediated organ damage may occur in the long run. The HBPM readings have a better association with adverse outcomes when compared to in-office BP readings. It is now recommended to use HBPM in the decision making algorithm as it predicts adverse outcomes better and also takes into account the white coat and masked hypertension.

Case 04	
About patient	40 years old man, BMI 29 kg/m2, active, Ambulatory Blood Pressure (ABP): overall 129/79 mm Hg, daytime 134/84 mm Hg, night-time 109/69 mm Hg; SBP load 10%, DBP load 7%, night time dip in BP >10%, BP in the first and last hour 145/80- and 150/85-mm Hg, respectively.
Question	Is he hypertensive? What are the targets for ABP? What is the advantage of ABP, if any?
Response	No, he is not hypertensive as his overall BP is 129/79 mm Hg. All other daytime, night-time readings are normal, his nocturnal dip is present and he has normal range BP load. Only his white coat window BP readings are in the hypertensive range, which means he has white coat hypertension. The ABP readings have a better association with adverse outcomes when compared to in-office BP readings, especially nocturnal BP readings. It is now recommended to use ABP in the diagnosis algorithm (wherever available) as it predicts adverse outcomes better and also takes into account the white coat hypertension (WCH) and masked hypertension (MH). It is also cost effective in the long run as it prevents the physician from over treating WCH and also not missing MH, as that would lead to HMOD and long term morbidity and mortality.

Case 05	
About patient	40 years old woman, BMI 27 kg/m2, sedentary, office BP taken in the assessment room unattended with automated oscillometric BP apparatus after rest of 5 minutes and average of 3 readings was 134/79 mm Hg while in-office BP using auscultatory method, the average of 2 readings was 150/80 mm Hg.
Question	Is she hypertensive? What are the targets for office BP auscultatory versus unattended automated office BP? What is the evidence in support of automated office BP?
Response	No, she is not hypertensive as her assessment room BP is 134/79 mm Hg (however, more readings are needed on separate visits). Her in-clinic office BP is in the hypertensive range and defines a white coat effect. The readings for the auscultatory BP in-clinic remain as 140/90 mm Hg Target for unattended automated oscillometric office BP (AOBP) that is taken out of the office in the assessment room is 135/85 mm Hg, as it is unattended. Data is scant for the unattended oscillometric office BP. The ACCORD, SPRINT trials have used it. SPRINT substudy showed AOBP was 7/6 mm Hg lower than daytime ABP. The results were variable and discordant with ABP.

Case 06	
About patient	47 years old woman comes to the clinic complaining of variable BP readings whenever BP is taken in the clinic. She talks non-stop and appears anxious with sweaty palms. Periods: 4/28 regular; mother menopause at the age of 55 years. BMI: 32 kg/m2, BP across 5 visits: 130/80 to 155/85 mm Hg
Question	The medical student attending the clinic inquires about factors that may give variable readings in this patient.
Response	Factors that can affect measurement of BP in this patient are: body habitus (obesity), cuff size, BP measurement protocol was not followed as patient was talking throughout, white coat effect as patient was anxious. Out of office modalities should be used like HBPM or ABP to circumvent the problem. If HBPM and/or ABP is not possible then repeated 4 or more readings in office after rest, and after explaining the method using appropriate cuff may get us a reading that is representative.

Case 07	
About patient	41 years old woman comes to the clinic complaining of raised BP readings whenever BP is taken outside the clinic. Her initial visit records an average OBP of 145/95 mm Hg. A second specific visit is scheduled, and x 3 readings are taken in office, the 1st reading is discarded and the latter 2 provides the average BP 145/90 mm Hg. BMI 25 kg/m2 and sedentary.
Question	What investigations can be ordered for her in this visit? What other investigations can be ordered?
Response	Basic tests for HTN screening: Creatinine, Electrolytes, FBS and/or HbA1c, Lipid profile, Urinalysis, ECG (12 lead), Funduscopy. Specific tests which are not ordered routinely: Echocardiogram only for those with LV dysfunction /HF/CAD, Urine albumin to creatinine ratio, Ankle brachial index.

Case 08	
About patient	43 years old man, 1st clinic visit BP was 155/90 mm Hg (pulse 88 bpm), BMI: 26 kg/m2, sedentary, HTN family history was positive for both parents when they were in 40's.
Question	Is this patient hypertensive? If not, then how do we rule him in or out for HTN?
Response	We need to plan a 1st visit then a specific visit after 4 weeks. We plan visits and readings according to protocol. Assess for HMOD. If SBP 140-179 mm Hg and no HMOD, DM, CKD one can wait. Lower threshold for diagnosis and treatment if HMOD, DM, CKD.

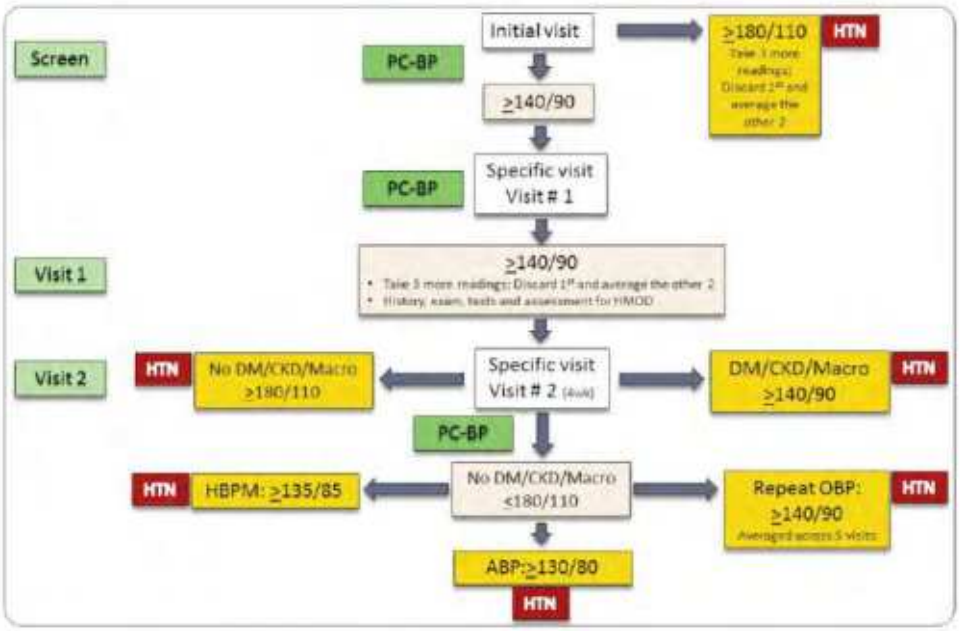

Figure-1: Diagnosis of Hypertension
PC-BP: post clinic BP, HMOD: hypertension mediated organ damage, OBP: office BP, HBPM: Home BP monitoring, ABP: Ambulatory BP monitoring, Macro: macro-vascular disease

Case 09	
About patient	40 years old man with family history of HTN, BMI: 27 kg/m2, active. Diet: high in refined carbohydrates, no fish or vegetables, high in meat. Undergone diagnostic protocol and is hypertensive with BP 150/90 mm Hg. No HMOD and ECG is within normal limits. Creatinine 1.1 mg/dL, FBS 105 mg/dL, HbA1c 6%, TC 180 mg/dL, TG 140 mg/dL, HDL-C 35 mg/dL, LDL-C 147 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-101 mmol/L, HCO3 24 mmol/L, urinalysis: normal. ASCVD risk: optimal risk 0.6%, current 10-year risk is 2% (low risk).
Question	What would be your treatment plan?
Response	Smoker, obese, sedentary, HMOD (retinal changes & LVH), creatinine borderline high, LDL is 167 mg/dL. Despite young age, the ASCVD 10-year risk for CV event is 18.6% which is very high compared to his optimal risk of 1.2%. Treatment plan: NPI + Drug treatment (simultaneous) and CT scan for Ca++ score. Target: Quit smoking, Weight loss (10 kg), LDL <100 mg/dL. If CT Ca++ score > 100, then ASA.

Case 10	
About patient	45 years old man, family history of HTN, smoker, BMI 28 kg/m2, sedentary. Diet: high in refined carbohydrates, no fish or vegetables, high in meat. Undergone diagnostic protocol and is hypertensive (BP 170/90 mm Hg). HMOD: HTN retinal change. ECG: sinus rhythm with LVH. Creatinine 1.3 mg/dL, FBS 105 mg/dL, TC 220 mg/dL, TG 140 mg/dL, HDL-C 30 mg/dL, LDL-C 167 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-101 mmol/L, HCO3 24 mmol/L, urinalysis: normal. ASCVD risk: optimal risk 1.2%; current 10-year risk. .18.6% (intermediate risk)
Question	What would be your treatment plan?
Response	Smoker, obese, sedentary, HMOD (retinal changes & LVH), creatinine borderline high, LDL is 167 mg/dL. Despite young age, the ASCVD 10-year risk for CV event is 18.6% which is very high compared to his optimal risk of 1.2%. Treatment plan: NPI + Drug treatment (simultaneous) and CT scan for Ca++ score. Target: Quit smoking, Weight loss (10 kg), LDL <100 mg/dL. If CT Ca++ score > 100, then ASA.

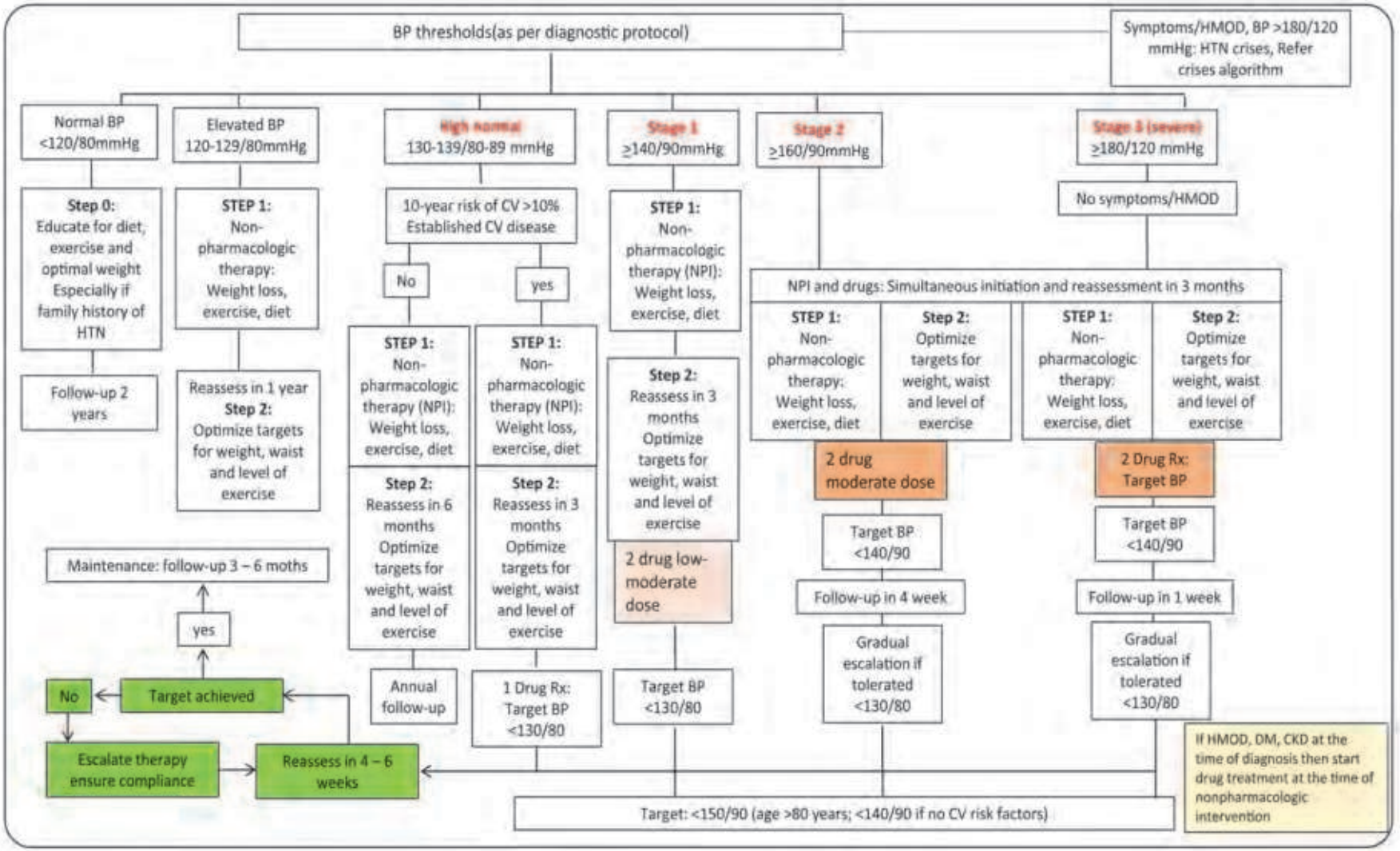

Figure-2: Threshold for treatment and plan for follow-up

Case 11	
About patient	45 years old man, family history of HTN, smoker, BMI 28 kg/m2, sedentary. Diet: high in refined carbohydrates, no fish or vegetables, high in meat. Undergone diagnostic protocol and is hypertensive (BP 170/90 mm Hg). HMOD: HTN retinal change. ECG: sinus rhythm with LVH. Creatinine 1.3 mg/dL, FBS 105 mg/dL, TC 220 mg/dL, TG 140 mg/dL, HDL-C 30 mg/dL, LDL-C 167 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-101 mmol/L, HCO3 24 mmol/L, urinalysis: normal. ASCVD risk: optimal risk 1.2%, current 10-year risk 18.6% (intermediate risk).18.6% (intermediate risk).
Question	What would be your treatment plan?
Response	Treatment plan: NPI + Drug treatment (simultaneous) / CT scan for Ca++ score. Medicines for BP 170/90 mm Hg: Moderate doses of two drugs; Long-acting ACEI/ARBs and long CCB. Follow-up 4 weeks and titrate doses. Further follow-up 4 weeks and addition of 3rd line. Target: BP <130/80 mm Hg, Quit smoking, Weight loss (10 kg), LDL <100 mg/dL (he is 67 mg/dL above target, would need NPI and statins). If CT Ca++ score >100, then ASA.

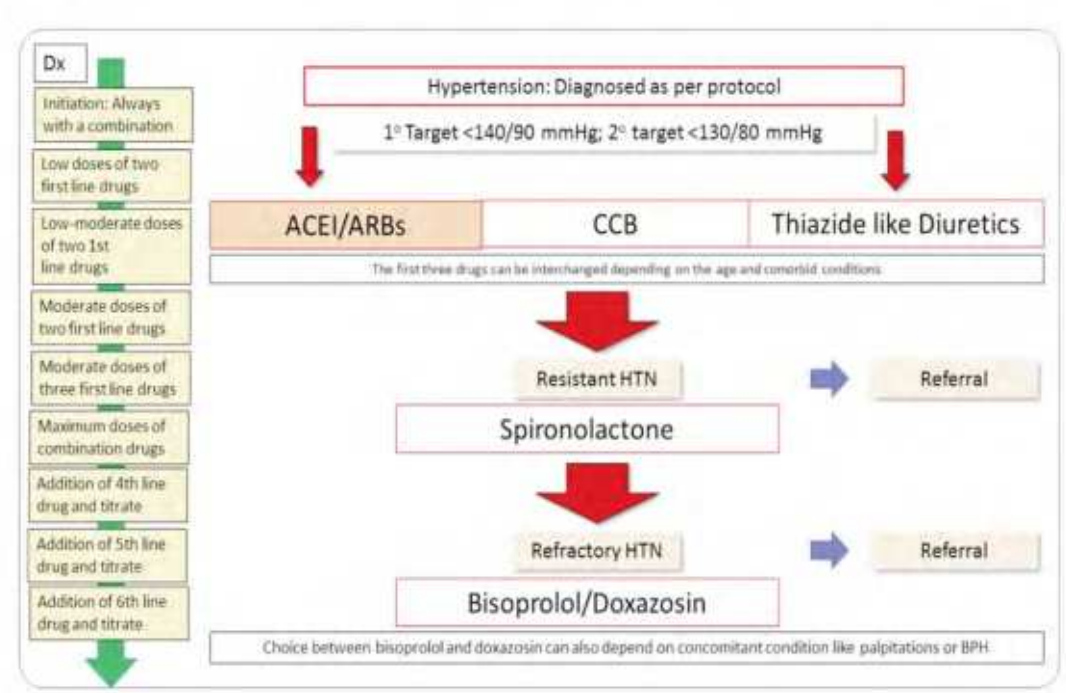

Figure-3: Drug therapy: ACD-SBD approach

Case 12	
About patient	43 years old man, family history of HTN, smoker, impaired fasting glucose, BMI 27 kg/m2, sedentary, Diet: high in refined carbohydrates. Undergone diagnostic protocol and is hypertensive (Clinic BP 145/87 mm Hg). HBPM 137/85 mm Hg and ABP overall 138/88 mm Hg. HMOD none. ECG with in normal range. Creatinine 0.7 mg/dL, FBS 129 mg/dL, HbA1c 7%, TC 157 mg/dL, TG 140 mg/dL, HDL-C 40 mg/dL, LDL-C 100 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-101 mmol/L, HCO3 24 mmol/L, urinalysis: protein 2+. ASCVD risk: optimal risk 0.9% and current 10-year risk 8.8% (intermediate).
Question	What would be your management plan?
Response	New onset DM with proteinuria. Treatment plan: NPI + Drug treatment (simultaneous) / CT scan for Ca++ score Medicines for BP 145/87 mm Hg: Low doses of two drugs; Long-acting ACEI/ARBs and long CCB. Follow-up 4 weeks and titrate doses. Further follow-up 4 weeks and addition of 3rd line. Target: BP 10 140/90 mm Hg, then 20 target <130/80 mm Hg, quit smoking, weight loss (10 kg), LDL <100 mg/dL. If CT Ca++ score > 100, then ASA and change LDL target to 50-70 mg/dL. **Note:** ALLHAT trial: all first line drugs are equally effective in BP lowering ADVANCE-BP and ACCOMPLISH trials showed combinations of ACEI/CCB and ACEI/D reduce CV events. In DM, comorbids play a role. In DM proteinuria, RAAS inhibitors are recommended as 1st line.

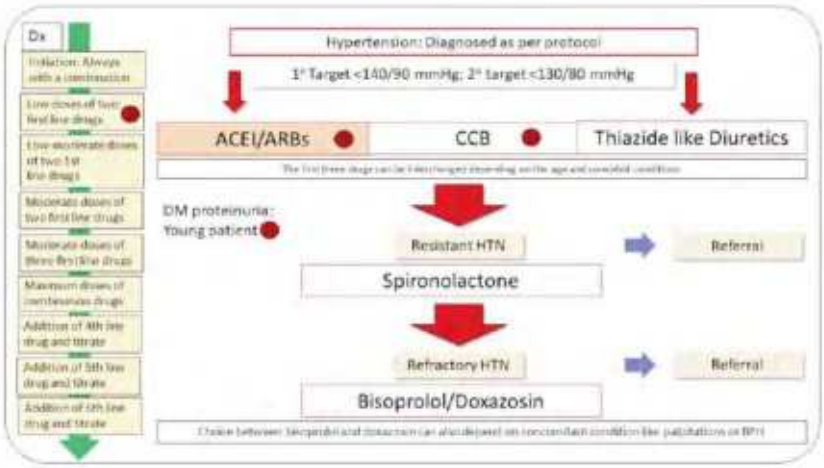

Figure-4: Drug therapy: ACD-SBD approach

Case 13	
About patient	65 years old woman, known hypertensive, routine follow-up for CAD, BP: (unattended AOBP) x 3 (190/115 mm Hg), BMI 28 kg/m2, sedentary, diet: normal, HMOD: prior MI, ECG: Qs in the inferior leads, Echo: EF 45%, SWMA (infero-posterior), LVDD II, Creatinine 0.7 mg/dL, FBS 102 mg/dL, HbA1c 6.1%, TC 190 mg/dL, TG 140 mg/dL, HDL-C 35 mg/dL, LDL-C 135 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-101 mmol/L, HCO3 24 mmol/L, urinalysis normal. Meds: ASA 751, Atorvastatin 20HS, Captopril 12.53, Atenolol 251, Aldactone 12.51.
Question	What would be your management plan for BP control? What if he now starts having typical chest pain within 24 hours?
Response	HTN with old MI (HTN crises: HTN urgency). No symptoms (HTN urgency) and if chest pain then (HTN emergency and will follow HTN emergency Rx). Treatment plan if no chest pain: NPI + Drug treatment. Does not require admission, no sublingual antihypertensive. Medicines for BP 190/115 mm Hg: Add or change to short acting drug e.g., captopril and up-titrate. Follow-up 24 – 72 hours and titrate doses. Long term consideration of changing ACEI/ARB to ARNI. Target: BP 10 140/90, then 20 target <130/80 mm Hg (gradually), weight loss (10 kg), LDL 50-70 mm Hg.

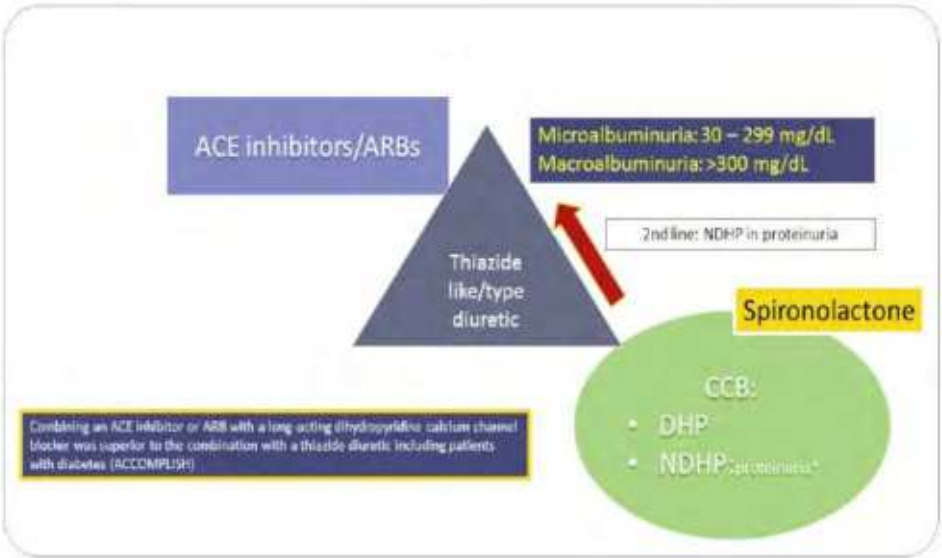

Figure-5: Treatment of HTN in DM
Weber MA, et al. J Am Coll Cardiol. 2010;56(1):77.*SHEP investigators. Curr Hypertens Rep. 1999;1(3):225 Case13

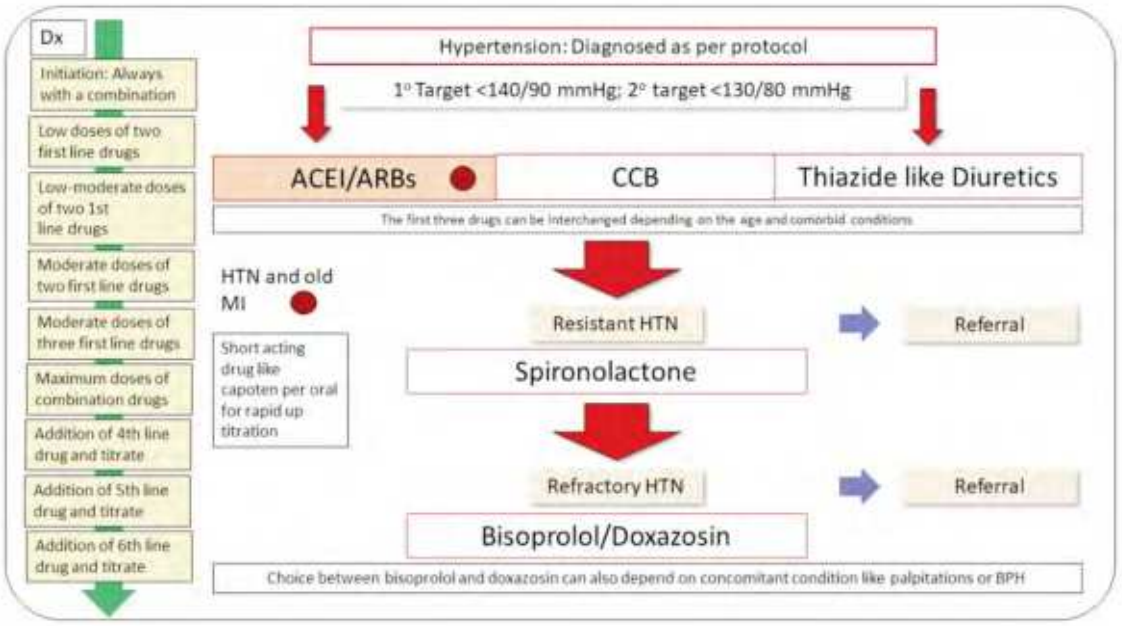

Figure-6: Drug therapy: ACD-SBD approach

National Hypertension Guidelines

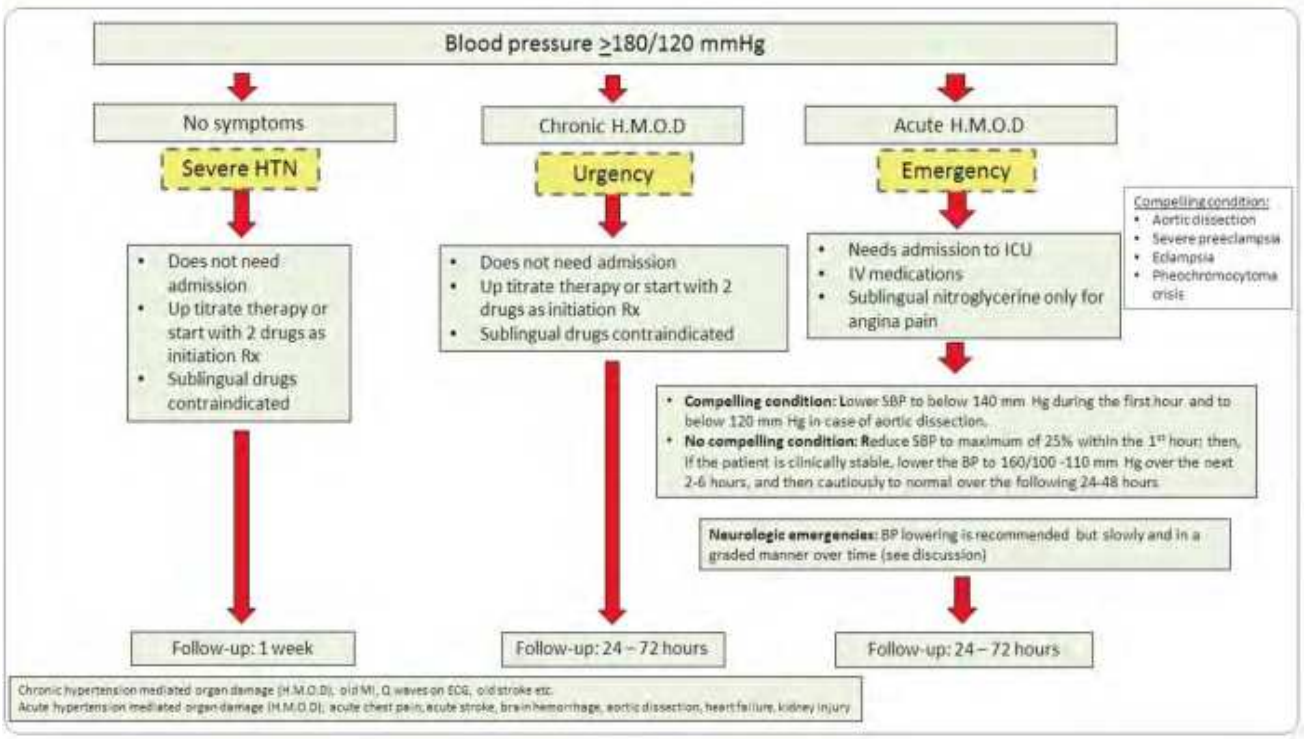

Figure-7: Management of Hypertension Crises

Case 14	
About patient	65 years old woman, known hypertensive, BP: (unattended AOBP) x 3 (150/95 mm Hg), BMI 28 kg/m2, sedentary, diet: normal, HBPM: 145/85 mm Hg and ABP: 150/88 mm Hg, HMOD: kidney, ECG within normal limits, Echo: EF 55%, LVDD 1, Creatinine 1.9 mg/dL, FBS 118 mg/dL, HbA1c 6.1%, TC 245 mg/dL, TG 220 mg/dL, HDL-C 35 mg/dL, LDL-C 180 mg/dL, Na+142 mmol/L, K+4.7 mmol/L, Cl-101 mmol/L, HCO3 18 mmol/L, urinalysis: proteinuria 3+ (albuminuria >250 mg/dL). Meds: Atenolol 251, Amlodipine 2.5.1
Question	What would be your algorithmic approach to initiating drug therapy?
Response	Figure 8 and Figure 9

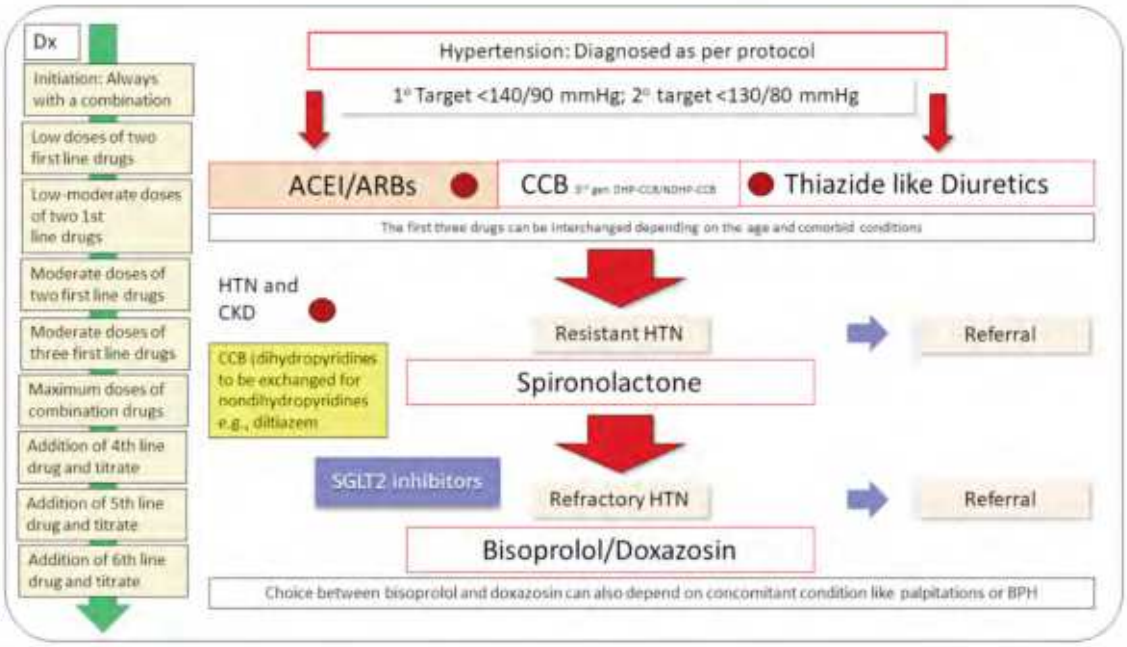

Figure-8: Drug therapy: ACD-SDB approach

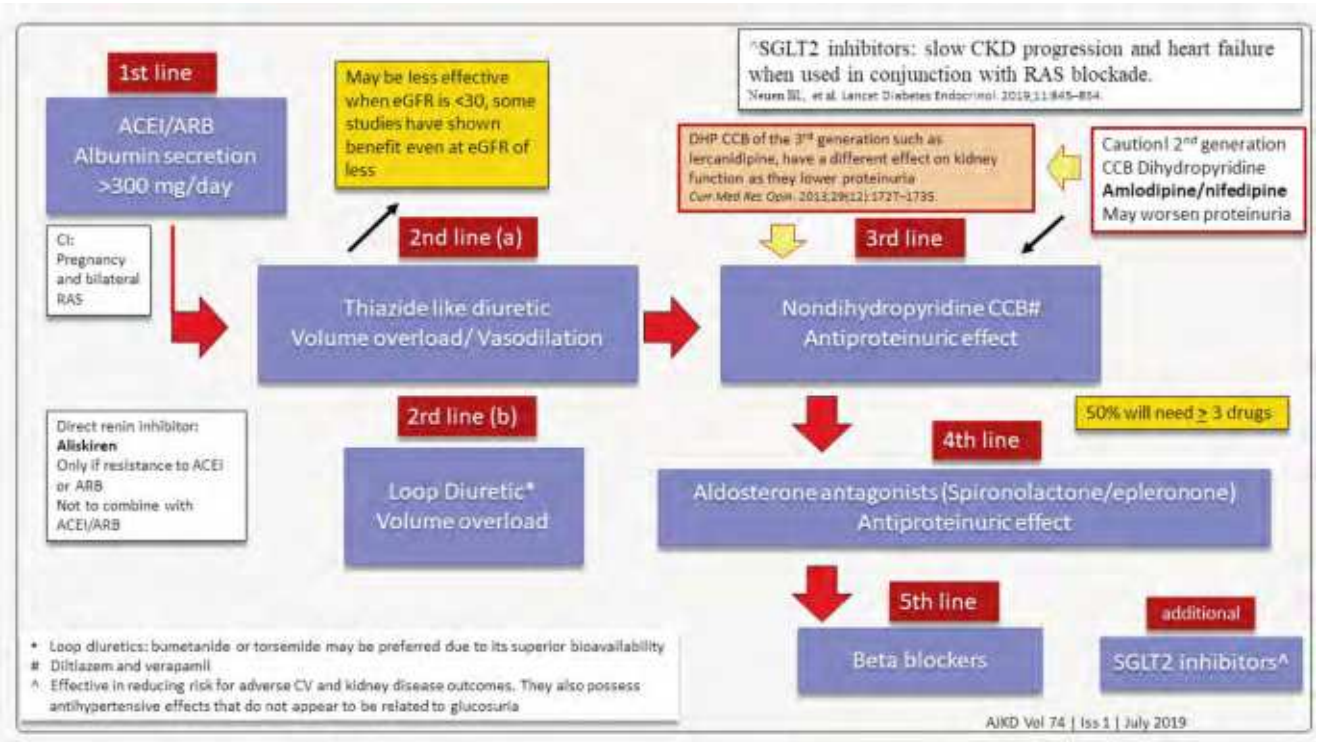

Figure-9: Drug therapy: step-wise approach

Case 15	
About patient	71 years old woman, known hypertensive, prior history of TIA (2 years ago) – lost to follow-up, sudden loss of movement on the left side, BP (attended AOBP) x 3 (170/100 mm Hg), BMI 30 kg/m2, sedentary, diet: normal, ECG: LVH with deep T wave inversion and QTc 490 ms, Echo: EF 55%, LVDD 1, Hb 16 g/dL, PLT 130,000, Creatinine 1.2 mg/dL, FBS 118 mg/dL, HbA1c 6.2%, TC 210 mg/dL, TG 190 mg/dL, HDL-C 30 mg/dL, LDL-C 160 mg/dL, Na+142 mmol/L, K+4.7 mmol/L, Cl-101 mmol/L, HCO3 18 mmol/L, urinalysis: protein 1+. Meds: Atenolol 25 1, HCTZ 25 1. CT scan: no bleed, old ischaemic changes.
Question	What would be your algorithmic approach to initiating drug therapy?
Response	In stroke prevention (primary): 1st stroke BP lowering is important, and some agents have shown to be of more benefit. For recurrent stroke BP lowering is important and particular data on drugs is not available in a randomized manner. Beta blockers drop BP. Beta blockers are hybrid agents for their duration of action, specific receptor blocking, hydrophilicity etc. and should be used accordingly. In the BPLTTC study BB were considered beneficial. Atenolol hydrophilic (crosses blood brain barrier) is short acting and does not cause vasodilatation.

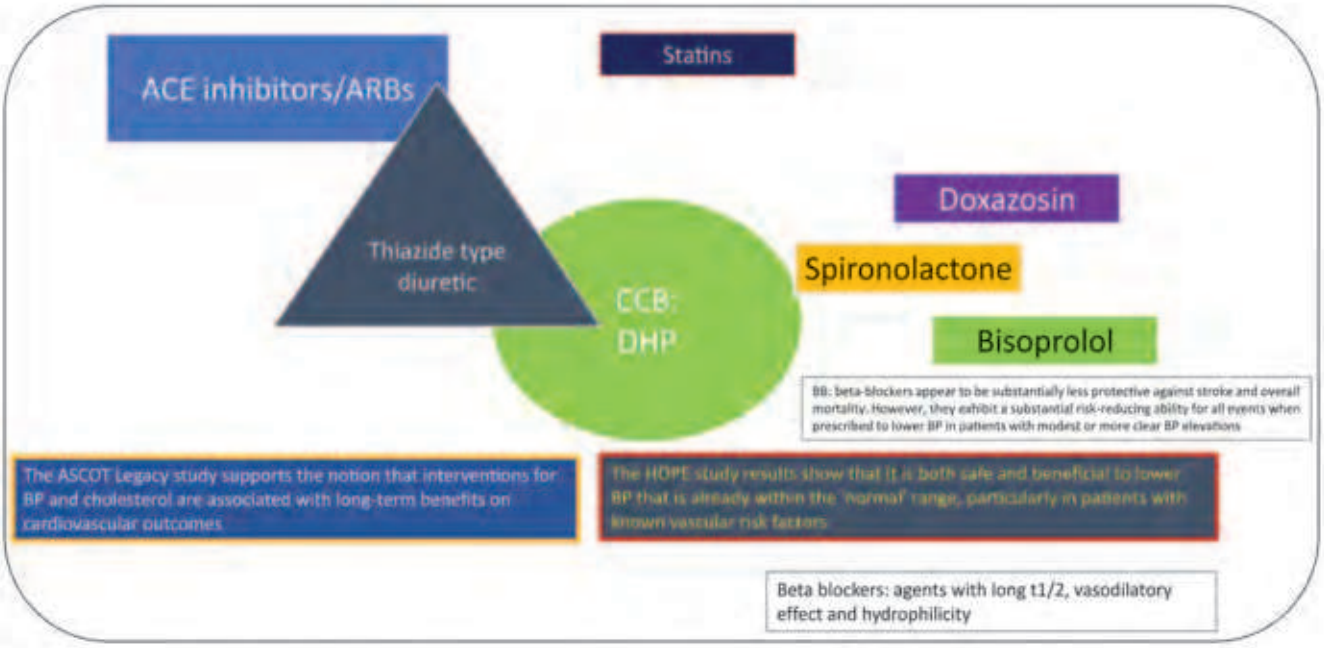

Figure-10: Treatment of HTN and prevention of stroke (1 and 2)
ASCOT trial investigators. Am J Cardiovasc Drugs. 2006;6(5):327-34. ASCOT Legacy study. Lancet. 2018 Sep 29;392(10153):1127-1137.
HOPE study. J Renin Angiotensin Aldosterone Syst. 2000 Mar;1(1):18-20. J Clin Hypertens (Greenwich). 2011;13;693–702.
Thomopoulos C, et al. J hypertens. 2020 ;38:1669-1681.

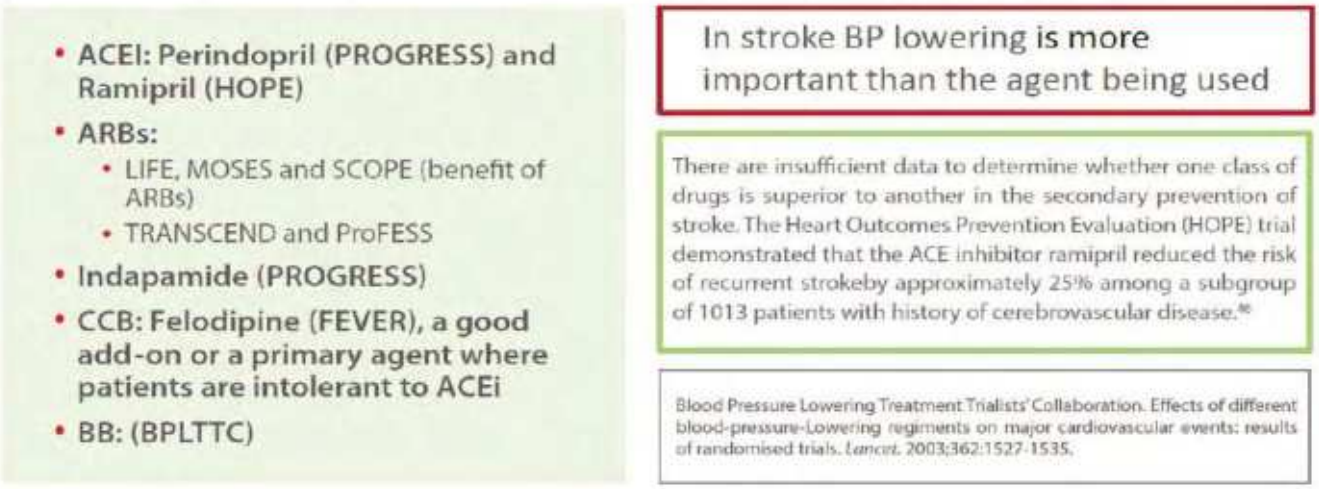

Figure-11: Treatment of HTN for stroke prevention
J Clin Hypertens (Greenwich). 2011;13;693–702

Case 16	
About patient	81 years old man, known hypertensive, on routine follow-up, BP 170/70 mm Hg, BMI 24 kg/m2, active, diet: normal, ECG: LVH with strain, Echo: EF 55%, asymmetric septal hypertrophy (15 mm), LVDD 1. Hb 12 g/dL, Creatinine 0.9 mg/dL, FBS 97 mg/dL, HbA1c 5.8%, TC 180 mg/dL, TG 190 mg/dL, HDL-C 30 mg/dL, LDL-C 160 mg/dL, Na+133 mmol/L, K+3.4 mmol/L, Cl-101 mmol/L, HCO3 30 mmol/L, urinalysis normal. Meds: Atenolol 251, HCTZ 25.1
Question	What would you look at in the clinic? What would be your approach to initiating and up titrating drug therapy?
Response	Hypertension in the elderly. Age 80 or more (target is <150/90 mm Hg). Check for postural drop in BP. Slow and gradual uptitration. Use ½ standard dose. We can use the first line therapy as in the general population. However, thiazide like/type diuretics tend to cause SBP reduction as compared to DBP, thus circumventing the wide pulse pressure issue in the elderly.

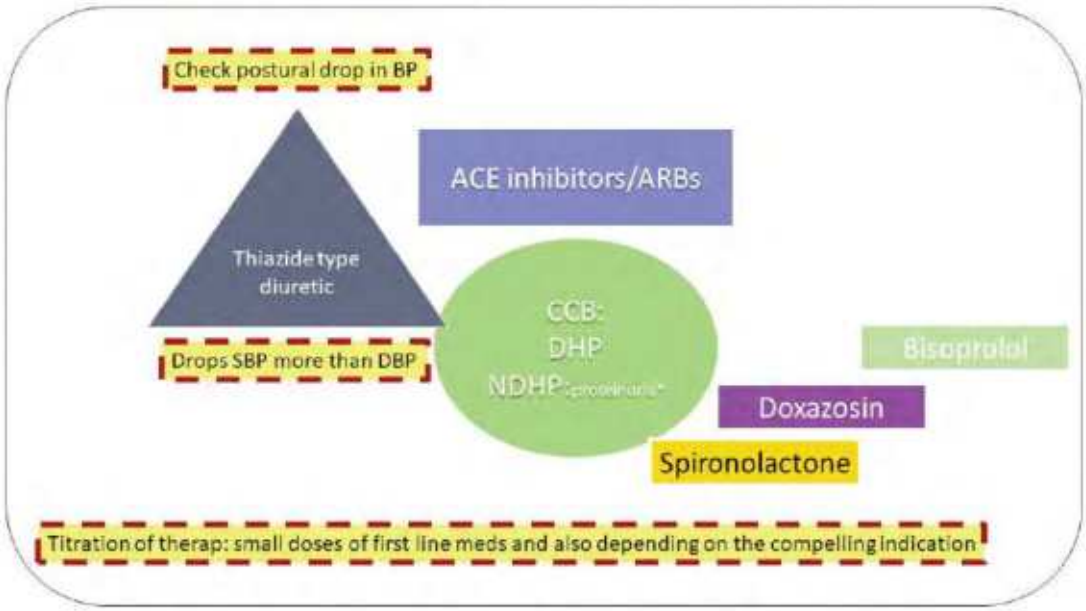

Figure-12: Treatment of HTN in a elderly patient

Case 17	
About patient	34 years old woman, 28 weeks gestation, the foetus is normal for dates, BP 150/90 mm Hg (average of 2 readings) 4 hours apart, sedentary, diet: rich in carbs and high in salt, ECG normal, Echo: EF 65%. Hb 14 g/dL, Creatinine 0.9 mg/dL, FBS 97 mg/dL, HbA1c 5.4%, TC 160 mg/dL, TG 150 mg/dL, HDL-C 40 mg/dL, LDL-C 100 mg/dL, Na+137 mmol/L, K+3.6 mmol/L, Cl-100 mmol/L, HCO3 28 mmol/L, urinalysis normal. Meds: none.
Question	Is she hypertensive? What parameter would you follow in the clinic? When and what would you use to control BP?
Response	Pregnancy, diet, exercise and Gestational HTN without proteinuria. Yes, she is hypertensive. Urinalysis is to be followed for proteinuria x weekly. Drug treatment only if BP >160/110 mm Hg. Treat with drugs only if BP less than 160/110 and more than 140/90 and additional risk factors. For chronic HTN patient who gets pregnant continue the prior Rx If it provides safety to both the mother and the baby.

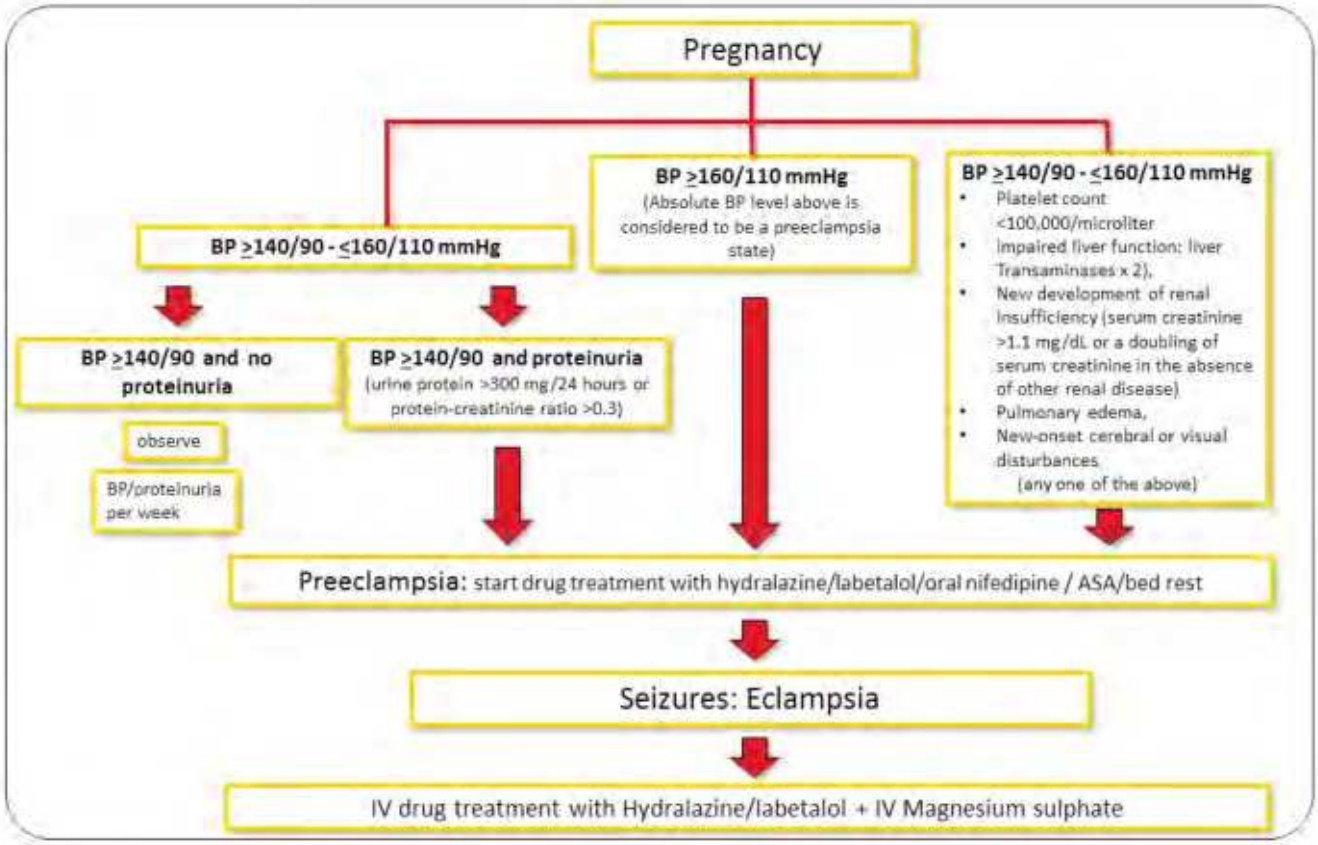

Figure-13: Algorithm for the management of Hypertension in pregnancy.

Case 18	
About patient	67 years old man, known hypertensive, on routine follow-up, BP 170/90 mm Hg (previously well controlled on moderate doses of 2 drugs), BMI 30 kg/m2, active, diet: standard Pakistani, ECG: within normal limits, Echo: EF 55-60%, mild asymmetric septal hypertrophy, LVDD 1. Hb 13 g/dL, Creatinine 0.9 mg/dL, FBS 97 mg/dL, HbA1c 5.7%, TC 220 mg/dL, TG 190 mg/dL, HDL-C 30, LDL-C 160 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-99 mmol/L, HCO3 27 mmol/L, urinalysis: normal. Meds: Telmisartan 80HS, HCTZ 251, Amlodipine 101
Question	What is this condition? How would you investigate? What would be the next drug to add?
Response	Uncontrolled BP on 3 drugs. Maximum doses of the three 1st line drugs. This is resistant hypertension, which is based on sodium. Drug for resistant hypertension is spironolactone. Eplerenone can be a substitute where spironolactone is not tolerated. At age 67 and sudden resistance to BP control should raise the possibility of atherosclerotic renal artery stenosis (RAS). Imaging to be done to rule out RAS. Refer to a specialist. ACEI/ARBs should not be prescribed in the fertile age and if on them, they should be changed.

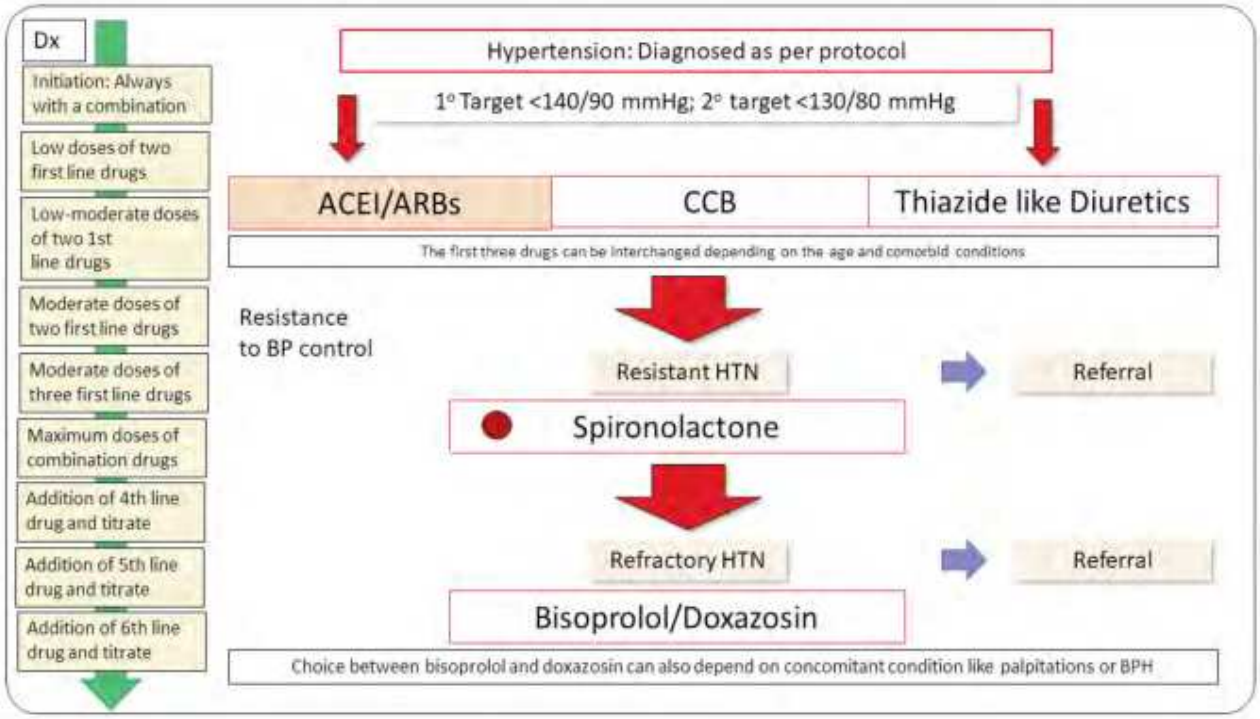

Figure-14: Drug therapy: ACD-SBD approach

Case 19	
About patient	57 years old man, known hypertensive, diabetic, on routine follow-up, BP 170/90 mm Hg, BMI 40 kg/m2, sedentary, Diet: foodie, ECG: within normal limits, Echo: EF 55-60%, mild asymmetric septal hypertrophy, LVDD 1. Hb 13 g/dL, Creatinine 0.9 mg/dL, FBS 122 mg/dL, HbA1c 6.8%, TC 220 mg/dL, TG 190 mg/dL, HDL-C 30 mg/dL, LDL-C 160 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-99 mmol/L, HCO3 27 mmol/L, urinalysis: protein trace. Meds: Atenolol 1001, HCTZ 12.5.1
Question	What precautions would you take in checking BP? What would you prescribe for the BMI? What would be your overall management approach?
Response	Hypertension with morbid obesity. Hypertension was found to affect 78.6% (76.6–80.7) of morbidly obese men and 66.0% (64.5–67.4) of morbidly obese women. (Booth HP, et al. Journal of Human Hypertension 2016; 30: 40–45.) Appropriate cuff size for BP monitoring. For BMI: Diet, Exercise (monitored exercise in a rehab programme), Drugs (in 1 year, loss of 3% to 12% more of their starting body weight than people in a lifestyle programme who did not take medication), Bariatric surgery. Follow the standard algorithm plus weight reduction. Rule out sleep apnea.

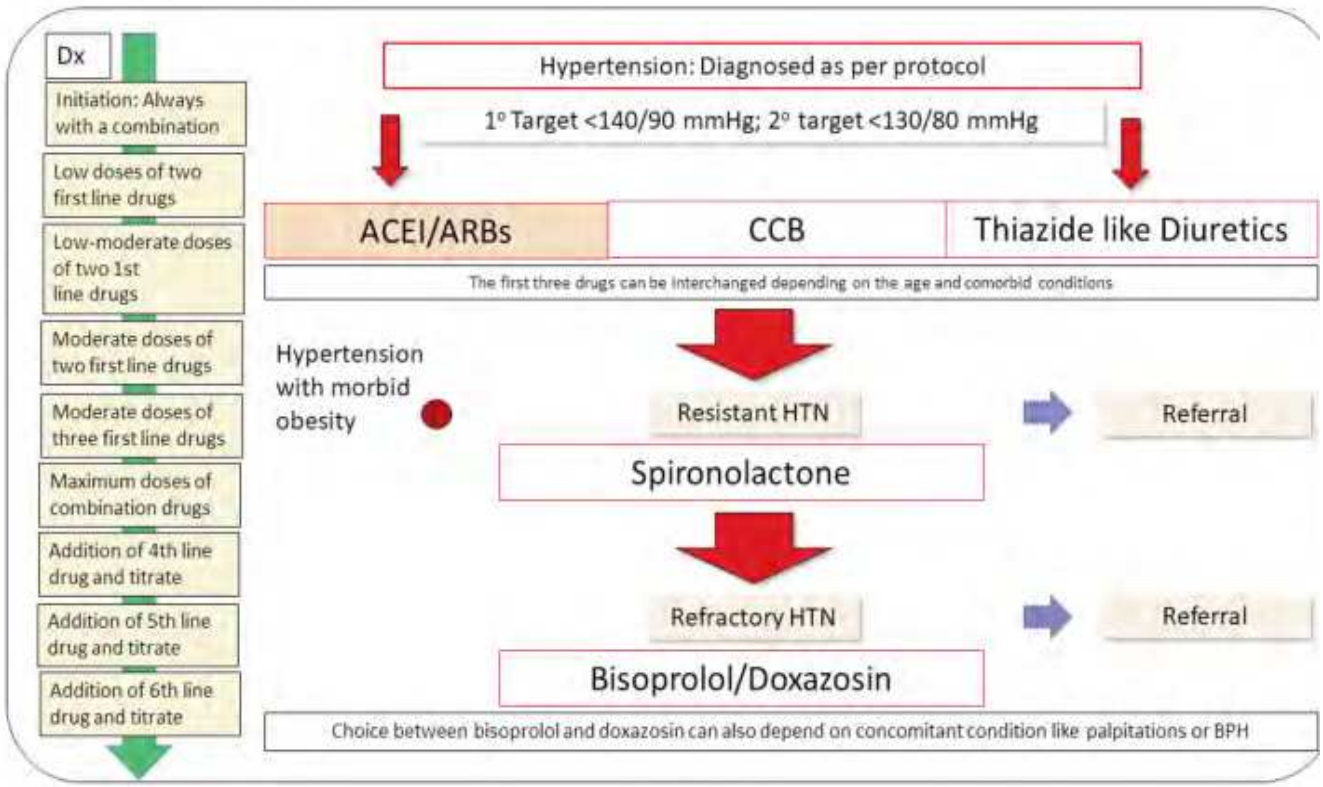

Figure-15: Drug therapy: ACD-SBD approach

Case 20	
About patient	57 years old man, known hypertensive and CHF, on routine follow-up, BP 150/95 mm Hg, BMI 25 kg/m2, sedentary, Diet: low salt, fluid restricted, ECG: sinus rhythm, LAHB, LBBB (QRS 150 ms), Echo: EF 30%, global hypokinesia, LVDD II, mild MR. Hb 11 g/dL, Creatinine 1.2 mg/dL, FBS 117 mg/dL, HbA1c 5.7%, TC 210 mg/dL, TG 160 mg/dL, HDL-C 30 mg/dL, LDL-C 140 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-99 mmol/L, HCO3 27 mmol/L, urinalysis normal, CT angiogram: normal coronary arteries, Ca++ score 0. Meds: Enalapril 52, Atenolol 251, Spironolactone 25.1
Question	What would be the drug management plan?
Response	HTN and CHF. ACEi can be replaced with ARNI. PARAMETER trial has shown more BP lowering compared to Olmesartan. The overall benefit of ARNI in CHF is well established. Four drugs that give mortality benefit; ARNI, BB, MRA, SGLT2i. Consider referral for device therapy.

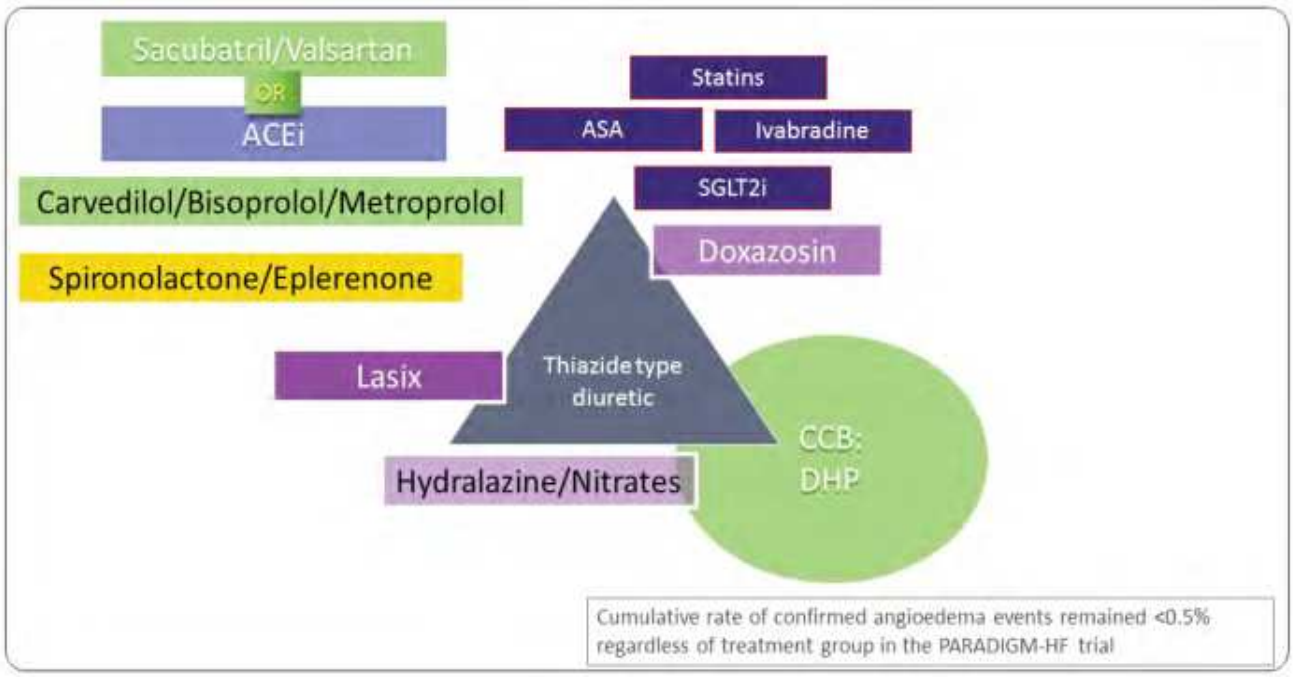

Figure-16: Therapy of HTN in a patient with CHF

ASCOT trial investigators. Am J Cardiovasc Drugs. 2006;6(5):327-34.
ASCOT Legacy study. Lancet. 2018 Sep 29;392(10153):1127-1137.
HOPE study. J Renin Angiotensin Aldosterone Syst. 2000;1:18-20. J Clin Hypertens (Greenwich). 2011;13;693–702.
Victor Shi, et al. International Journal of Cardiology 264 (2018) 118–123

Case 21	
About patient	37 years old man, known hypertensive, active, diet: careful about diet, BMI 23 kg/m2, BP 130/80 mm Hg (average reading across many clinic visits), strong family history of HTN (mother at age 35). Complaint: Ankle swelling, dry hacking cough and pain in the periareolar region. Meds: Perindopril 4,2 Indapamide 1.5SR,1 Amlodipine 10,1 Spironolactone 25.1
Question	What are the reasons for his symptoms? How would you circumvent this problem?
Response	These are most likely due to side effects of the drugs being used; Dry hacking cough due to ACE inhibitors, Ankle oedema due to dihydropyridine CCB and Periareolar pain due to spironolactone. Change the drugs to evidence-based alternatives. Perindopril 42, Indapamide 1.5 SR1, Amlodipine 101, Spironolactone 251 Perindopril to long-acting ARB. Amlodipine to lercanidipine or decrease dose of amlodipine to 5 mg. Spironolactone to eplerenone (periareolar pain and gynecomastia is aound 10% in spironolactone and 0.5% in eplerenone*). Other drugs to consider: Doxazosin, bisoprolol. (*The RALES trial revealed that spironolactone caused gynecomastia and breast pain in 10% of HF patients whereas only 0.5% of HF patients on eplerenone in the EPHESUS trial). Pitt B, et al. N Engl J Med 1999;341:709-17. Sasano H, et al. N Engl J Med 2003;348:1309-21.

Case 22	
About patient	43 years old woman, sedentary, diet: foodie, BMI 27 kg/m2, BP 160/80 mm Hg (average reading across many clinic visits). Hb 13 g/dL, Creatinine 0.9 mg/dL, FBS 109 mg/dL, HbA1c 6.3%, TC 220 mg/dL, TG 190 mg/dL, HDL-C 30 mg/dL, LDL-C 160 mg/dL, Na+139 mmol/L, K+4.1 mmol/L, Cl-99 mmol/L, HCO3 27 mmol/L, urinalysis: normal. Started on treatment: Atenolol 501 and HCTZ 25.1
Question	Are you concerned about the drug treatment? What would you suggest for ideal drug plan?
Response	Drug combination. Yes, concerned about Dx combo. BMI (overweight). Beta blocker and diuretic combination can cause new onset DM. Subjects with new-onset DM and those with a previous DM are almost 3-times as likely to have subsequent CVD. The following two references will help in building further understanding. Verdecchia P. et al. Hypertension. 2004; 43:963-969. Giuseppe M, et al. ESC/ESH 2007 guidelines. European Heart Journal."

Case 23	
About patient	37 years old woman, married, strong family history of HTN (mother at age 35), active, diet: generally healthy, BMI 32 kg/m2, Clinic BP 138/84 mm Hg, HBPM: 134/84 mm Hg, ABP: overall 142/83 mm Hg, day 130/81 mm Hg, night 155/85 mm Hg.
Question	How would you interpret her BP information? What would be your management plan?
Response	Interpretation of BP: check clinic BP, cuff size (BMI 32), clinic BP: borderline, home BP: high normal, ABP overall: HTN range, ABP daytime: normal, ABP night time: Hypertension range. Overall interpretation is masked HTN with reversed nocturnal dip (HTN). Management plan: Sleep study to rule out OSA. NPI and work to targets and Drug management.

Case 24	
About patient	47 years old man, recent NSTEMI (2 weeks), strong family history of HTN (mother at age 35), active, diet: generally healthy, BMI 24 kg/m2, Home BP: 145/90 mm Hg, ECG: Sinus rhythm with T wave inversion V1 to V5, Echo: EF 55%. Hb 14 g/dL, Creatinine 0.9 mg/dL, FBS 97 mg/dL, HbA1c 5.4%, TC 180 mg/dL, TG 150 mg/dL, HDL-C 40 mg/dL, LDL-C 120 mg/dL, Na+137 mmol/L, K+3.6 mmol/L, Cl-100 mmol/L, HCO3 28 mmol/L, urinalysis: normal.
Question	What would be BP management plan?
Response	Recent ACS. NPI (cardiac rehab – 36 sessions give mortality benefit). Drug Rx remains the same but BB move up as first line therapy, as it provides mortality benefit and should be part of the regime for at least 1 year. If there is LV dysfunction then ARNI and SGLT2i will also be considered.

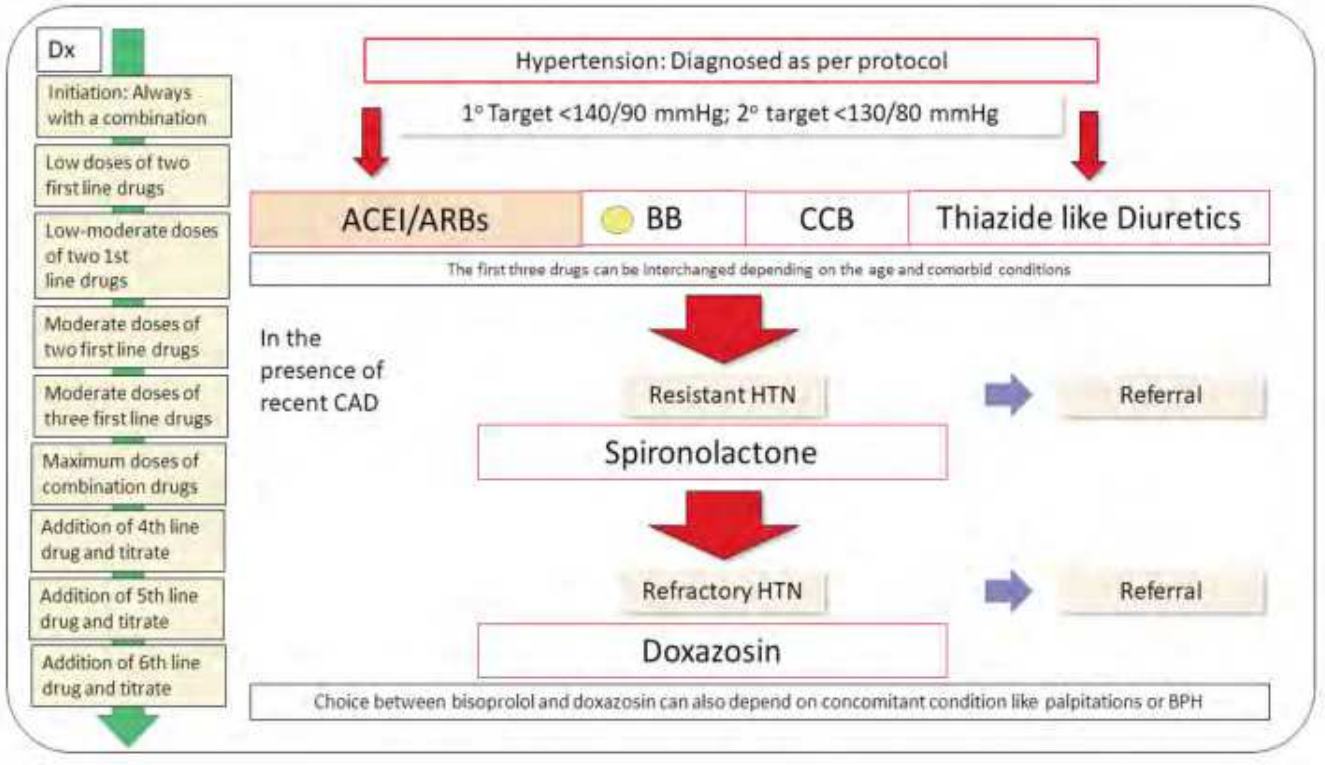

Figure-17: Drug therapy: ACD-SBD approach

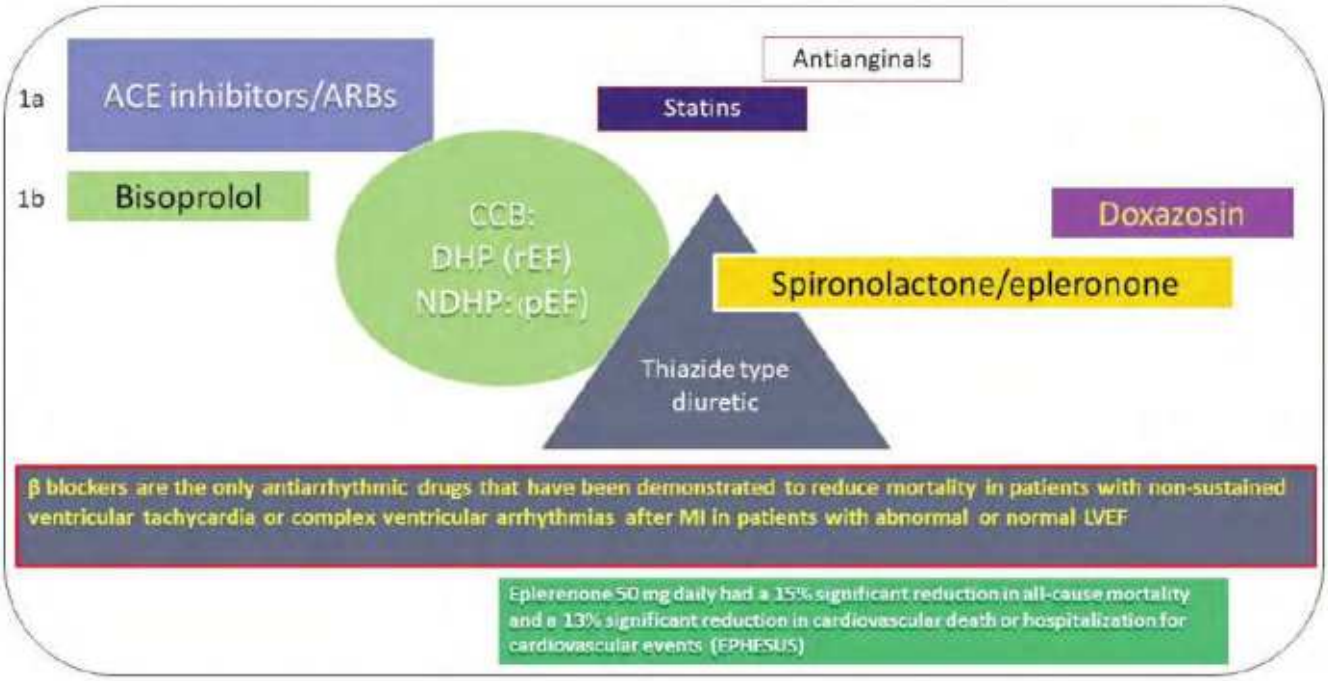

Figure-18: Therapy of HTN post myocardial infarction
Am. J. Cardiol. 74(7), 674–680 (1994)
Am. J. Cardiol. 74(3), 267–270 (1994).
J. Am. Coll. Cardiol. 71(6), e127–e248 (2018).

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