2020 Clinical Practice Guidelines for the Management of Hypertension in the Philippines

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STATEMENT OF INTENT

This guideline is meant for the clinical management of hypertension, based on the best available evidence at the time of its development and is designed to be a guide for clinicians in managing hypertension for the Filipino patient. This, however, should not replace sound clinical judgment by doctors and the ultimate decision for treatment should involve both clinician and the patient.

REVIEW OF THE GUIDELINES

These guidelines issued in December 2020, will be reviewed in 5 years (2025) or sooner if significant new evidence becomes available.

FUNDING and CONFLICTS OF INTEREST

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file . Any changes in declarations of interest that arise during the writing period were notified to the Philippine Society of Hypertension (PSH) and the Philippine Heart Association (PHA) and updated.

These guidelines were funded by the PSH and the PHA without any involvement from the healthcare industry. Moreover, these organizations did not influence the development of the recommendations.

CPG Secretariat
Philippine Society of Hypertension and Philippine Heart Association

Electronic version is available on the following websites:

https://www.philippinesocietyofhypertension.org.ph

http://www.philheart.org

TERMS OF REFERENCE

GUIDELINE DEVELOPMENT

The development of the Philippine Practice Guideline for Hypertension was spearheaded by the Philippine Society of Hypertension and the Philippine Heart Association, in collaboration with experts from various fields including pediatricians and pediatric cardiologists, obstetrician-gynecologists, endocrinologists, nephrologists, and neurologists/stroke specialists. A steering committee was nominated, and they organized a technical writing group (TWG) comprised of these experts who decided in consensus to use the ADAPTE process in developing the 2020 Clinical Practice Guidelines (CPG) on Hypertension.

Each of the organizations involved in the process of guideline development nominated a group of experts who will comprise the technical working group (TWG). The TWG was organized into clusters that developed the six areas that were covered by the CPG:

1. General recommendations for adults with hypertension
2. Blood pressure management among persons with diabetes
3. Blood pressure management among persons with chronic kidney disease
4. Blood pressure management among persons with stroke

5. Hypertension among Pregnant women
6. Hypertension in children.

The TWG came up with 30 clinical questions that are usually asked by clinicians, patients and stakeholders which were previously gathered during workshops and webinars held by the medical societies involved.

The TWG searched for all published guidelines, both local and international, pertaining to the clinical questions, with the use of electronic search engines and manual search. Literature search was done by each TWG member using search engines such as PubMed (Medline), Google Scholar, other medical previous engines using key words relevant to each clinical question. All literature that was retrieved were appraised, presented, and discussed during TWG meetings. The full listing of guidelines that were retrieved, appraised, and included for each research question for each of the TWG clusters is found in the Appendices.

Each cluster developed and presented their draft recommendations for approval to the external panel of experts for discussion and approval by consensus of the majority. These draft recommendations were then revised and presented again to the panel and were finalized. Several public presentations have also been made to further elicit feedback from various stakeholders including patients on the details of the guidelines. These guidelines were also presented to the Department of Health for their review and approval. The recommendations in this manuscript are the result of these processes.

OBJECTIVES OF THE GUIDELINES

The main objective of these guidelines is to present evidence- based recommendations that are adapted from international practice guidelines taking into consideration the local context and practice of doctors in the Philippines.

Target Population:

The guideline aims to help physicians make sound clinical decisions in the management of hypertension and presents the latest information about the diagnosis, treatment thresholds and blood pressure targets, appropriate medications, and specific management of hypertension among individuals with uncomplicated hypertension, hypertension among those with diabetes, stroke, chronic kidney disease, as well as the hypertension among pregnant women and pediatric populations. It also includes statements on the appropriate screening and monitoring when managing hypertension, and identification of groups who are at high risk for cardiovascular (CV) events.

Target Audience:

These guidelines are developed for physicians in general practice but is also useful for all healthcare professionals in the Philippines.

Clinical Questions

<u>General Questions on Managing Hypertension among Adults Aged 19 years old and above</u>

1. Among adult Filipinos 19 years old and above, what is the definition of hypertension?

2. Among adult Filipinos, what device is recommended for accurate blood pressure determination and monitoring?

3. Among Filipinos, what are the blood pressure targets among adult hypertensive Filipinos for the prevention of cardiovascular disease?

4. Among Filipino hypertensive patients, what are the available treatment options?

    4.1. What non-pharmacologic therapy is recommended for persons with hypertension?

    4.2 What are the preferred drugs for the treatment of hypertension among Filipinos for prevention of cardiovascular diseases?

Hypertension among Adults with Diabetes

5. Among persons with diabetes, what is the threshold for (pharmacologic) treatment of elevated blood pressure?

6. Among persons with diabetes and hypertension, what non-pharmacologic therapy is recommended?

7. Among persons with diabetes and hypertension, what are the blood pressure targets for prevention of cardiovascular diseases (mortality and morbidity)?

8. Among persons with diabetes, what are the preferred drugs for the treatment of hypertension?

Hypertension Management among Persons with Chronic Kidney Disease (CKD)

9. Among patients with CKD, what is the level of blood pressure to start pharmacotherapy to prevent cardiovascular complications and renal progression?

10. Among patients with CKD who are pre-dialysis, what is the target blood pressure to prevent cardiovascular complications and renal progression?

11. Among patients with CKD, what is the level of blood pressure to start initiation with two antihypertensive drugs to prevent cardiovascular complications and renal progression?

12. Among patients with CKD, what is the anti-hypertensive of choice to prevent cardiovascular complications and renal progression?

13. Among patients with CKD with albuminuria/proteinuria, what is the anti-hypertensive of choice to prevent cardiovascular complications and renal progression?

14. Among patients with CKD with resistant hypertension, is addition of mineralocorticoid receptor antagonist beneficial in reducing albuminuria and cardiovascular events?

15. Among patients with CKD, is giving anti-hypertensive at bedtime more beneficial in reducing cardiovascular event?

Hypertension Among patients with Stroke

16. 1 For adults with acute ischemic stroke (AIS) who are eligible for intravenous (IV) thrombolysis but not for mechanical thrombectomy, what is the threshold for pharmacological treatment and the target blood pressure (BP)?

16.2 For adults with AIS who are eligible for IV thrombolysis but not for mechanical thrombectomy, what are the pharmacologic agents of choice to reach the target BP?

17.1 For adults with AIS who are eligible for mechanical thrombectomy (with or without IV thrombolysis), what is the threshold for pharmacological treatment and the target BP?

17.2 For adults with AIS who are not eligible for IV thrombolysis or mechanical thrombectomy, what pharmacological agent may be used to achieve target BP, when needed?

18.1. For adult patients with acute hypertensive parenchymal intracerebral hemorrhage (ICH), what is the threshold for BP lowering in the first few hours upon presentation at the emergency room?

18.2 What are the pharmacologic agents of choice and manner of administration?

19.1 For adults who have a history of stroke, what is the target blood pressure level for secondary prevention?

19.2 What would be the target BP when lowering the blood pressure in acute intracranial hemorrhage (ICH)?

19.3 What is/are the pharmacologic agent/s of choice and manner of giving it/them?

20. For adults who have a history of stroke, what is the target blood pressure level for secondary prevention?

Hypertension Among Pregnant (and Lactating) Women

21. What are the different types of hypertensive disorders of pregnancy (HDP) and what are the criteria for each?

22. What antihypertensive agents can be used for urgent blood pressure control in pregnancy?

23. When do we treat hypertension during pregnancy?

24. What are the pharmacologic treatment options?

25. How is hypertension managed during the immediate postpartum and breastfeeding periods?

Hypertension Management Among Children

26. Among pediatric patients, what is the threshold for commencing pharmacologic treatment for hypertension?

27. What advice regarding nonpharmacologic treatment is recommended for pediatric patients?

28. What are the BP targets for prevention of target organ complications?

29. What are the preferred medications for children?

30: What is the recommended technique and BP device for accurate BP measurement in pediatric patients?

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BACKGROUND

The 2020 Clinical Practice Guidelines (CPG) in the Management of Hypertension is a collaboration of the different medical societies whose main goal is to manage hypertension in the country. These are the Philippine Heart Association (PHA), Philippine Society of Hypertension (PSH), Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM), Philippine Neurology Association (PNA) and Philippine Society of Nephrology (PSN). The need to manage the pediatric and pregnant populations was considered an important gap that needs to be addressed, thus the Philippine Pediatric Society (PPS) and the Philippine Obstetrics and Gynecological Society (POGS) were called to help create the guidelines. A technical working group composed of cardiologists, clinical epidemiologists, hypertension specialists, endocrinologists, nephrologists, neurologists, pediatricians, and obstetricians reviewed and adapted existing guidelines, critically appraised relevant literature, and finally created a consensus on the clinical statements taking local practice into consideration.

It is the hope of this 2020 CPG that the Filipino physician may use the recommendations confidently in caring for most patients and is meant to guide practices that meet the needs of patients. The ultimate decision must be made by the physician and patient together and should not be a replacement for clinical judgment.

The rationale for guideline adaptation rather than de-novo guideline development is to allow the efficient use of current information that is already available in existing practice guidelines, abbreviating the process of identifying individual studies that apply to specific research questions, appraising them, evaluating individual study quality and finally, developing specific recommendations.

SCOPE OF THE GUIDELINES

The scope of this CPG includes statements on the definition of hypertension, the target BP threshold, the appropriate medications needed to reach targets, and managing the diabetic, stroke, chronic kidney disease, pregnant, and pediatric populations. It also includes statements on the appropriate screening and monitoring when managing hypertension, and determination, identification of high-risk groups for cardiovascular (CV) events which will be targeted for prevention and treatment.

Only major classes of locally available medications are mentioned, focusing on those that are widely used in practice, and those that would provide the most benefit in terms of CV risk reduction. Furthermore, clinical questions that were most relevant to clinical practice were identified, as well as the applicability of recommendations to local clinical scenarios.

EPIDEMIOLOGY

The Philippines has shown an increasing trend of individuals afflicted with elevated blood pressure as shown in a survey by the Philippine Heart Association. The PRESYON-3[1], which is a prospective, multi-staged, stratified, nationwide survey on hypertension conducted in 2013, the prevalence of hypertension in Filipino adults aged more than 18 years old was 28%. More than half of the hypertensive individuals, about 54%, were elderly, defined as ≥ 60 years old. The survey also captured about 1% hypertensives in the pediatric population, ages 12-18 years old. In the survey, 75% of hypertensives were receiving medications and the most common drug prescribed by physicians is a beta-blocker followed by a calcium channel blocker. About 75% are maintained on a single pill medication while 21% were on two medications and about 4% were on three medications. However, despite the increased awareness of Filipino individuals about their disease, we see a high percentage of uncontrolled hypertensive individuals. Eighty percent of patients have their blood pressure uncontrolled compared to individuals who were on target blood pressure[1].

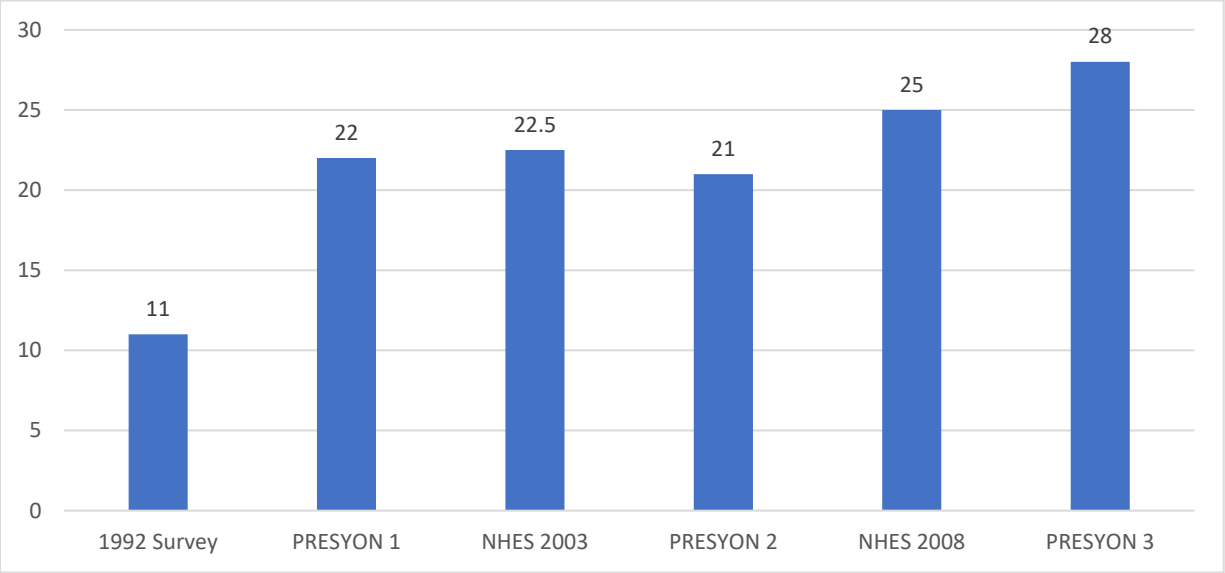


Figure 1. Prevalence of Hypertension in Adults (> 18 years old) based on Local Surveys

The latest Expanded National Nutrition Survey (eNNS)[2] conducted by the Food and Nutrition Research Institute (FNRI) in 2018 showed a downward trend in hypertension prevalence in the country. There was a decline in the number of hypertensive individuals, from 23.9% in 2015 to 19.2% in 2018. The concerted effort of the government, medical societies, physicians, and patients in prioritizing non-communicable diseases (NCD) programs may have brought the downward trend in hypertension prevalence.

The prevalence of childhood hypertension is increasing with approximately 3.5% of children having HTN and approximately 2.2% to 3.5% having elevated blood pressure (BP).[1,2] Obesity is a significant factor in this increase in prevalence. Elevated BP in childhood increases the risk for adult HTN and cardiometabolic disease. Unfortunately, there are only a few local data on childhood hypertension.

METHODOLOGY OF GUIDELINE DEVELOPMENT

The ADAPTE process was utilized in developing the 2020 CPG on Hypertension. The development and updating of high-quality practice guidelines require substantial resources. To produce these guidelines in a shorter time and limited resources, guideline adaptation has been proposed as an option for guideline development. The ADAPTE process provides a systematic approach to adapting guidelines produced in one setting for use in a different cultural and organizational context. The process has been designed to ensure that the adapted guideline not only addresses specific health questions relevant to the context of use but also is suited to the needs, priorities, legislation, policies, and resources of the targeted setting. The process has been developed to meet the needs of different user groups including guideline developers, health care providers and policy makers. The transparent and explicit reporting of the adaptation process followed will enhance the quality and validity of the adapted guideline.

The ADAPTE process consists of three main phases, each with a set of modules:

1. Set-up Phase – outlines the necessary tasks to be completed prior to beginning the adaptation process, for example identifying the necessary skills and resources.
2. Adaptation Phase – assists users through the process of selecting a topic to identifying the health questions; searching for and retrieving guidelines, assessing the consistency

of the evidence and guideline quality, currency, content, and applicability; decision making around adaptation; and preparing the draft adapted guidelines

3. Final Phase – guides the user through the process of obtaining feedback on the document from stakeholders impacted by the guideline, consulting with the developers of source guidelines in the adaptation process, establishing a process for the review and updating of the adapted guideline and creating a final document[3].

SET-UP PHASE

Each of the collaborating organizations first organized themselves by identifying officers who will be members of the steering committee. This group was in-charge of the administrative aspects of the guideline development including helping to identify and then vetting clinical questions, setting timelines, and tapping internal (from the organizations) funding sources which will be used for various aspects of the activity. They also coordinated with other organizations for guideline dissemination.

Each of the organizations involved in the process of guideline development also nominated a group of experts who will comprise the technical working group (TWG). The TWG was organized into clusters that developed the six areas that were covered by the CPG: general recommendations for adults with hypertension; blood pressure management among persons with diabetes, chronic kidney disease; and stroke; and hypertension among pregnant women and children.

Each of the members of the steering committee (SC) and the TWG accomplished and submitted a declaration of conflicts of interest (COI) form before the start of the guideline development, which is summarized in Appendix 1. None of the members of the SC and the TWG had significantly COI such as employment by pharmaceutical companies or governmental agencies that are involved in the approval of drugs, or of guidelines for the use of drugs, or devices. The members of the SC reviewed each of the submissions and decided on whether there was significant conflict of interest.

ADAPTATION PHASE

Literature Search. The TRC searched for all published guidelines until January 2020, both local and international, pertaining to the clinical questions, with the use of electronic search engines and manual search. The literature search was conducted using the search engines PubMed,

Scopus, Medline, Google Scholar, other medical engines using key words relevant to each clinical question. Unpublished data were also retrieved, whenever possible.

Development of Guideline Recommendations and Evidence summaries. Using the evidence summaries and data gathered by the published guidelines, draft guideline recommendations and evidence summaries were then developed by the TWG. Each cluster developed and presented their draft recommendations to the members of the TRC and the steering committee for comments and approval by a consensus of the majority and were subsequently modified as needed.

Consensus Building/Final Phase. These guideline recommendations were then subjected to external review by a panel of experts representing local stakeholders in the care of hypertension. The results of the panel meetings are presented here as the final recommendations. While lay persons were not specifically invited to the consensus meetings, their voice was represented by clinicians who in their practice regularly interact with persons with hypertension. More directly, during the public fora where the guideline was disseminated, physicians who had hypertension and even lay individuals who had hypertension were able to interact with the guideline developers and give feedback.

DISSEMINATION AND IMPLEMENTATION OF GUIDELINES

The 2020 CPG guidelines has been disseminated in the different meetings of the main stakeholders of the guidelines. The final paper will also be available for download in the websites of the Philippine College of Physicians (PCP), PSH, PHA, PSEDM, PNA, PSN, PPS and other relevant medical societies in the Philippines. The executive summary has been published in the Journal of Clinical Hypertension and is cited as follows: Ona DID, Jimeno CA, Jasul GV, et al. “Executive Summary of the 2020 Clinical Practice Guidelines for the Management of Hypertension in the Philippines.” J Clin Hypertension. 2021;1–14. https://doi.org/10.1111/jch.14335

STATEMENTS FOR THE MANAGEMENT OF HYPERTENSION

I. Diagnosis and Management of Hypertension in Adult Population

Clinical Question 1. Among adult Filipinos 19 years old and above, what is the definition of hypertension?

Statements

1.1 Hypertension is defined as an office blood pressure (BP) of 140/90 mmHg or above, typically taken at least twice on two separate days.

1.2 It is recommended that office BP be used to classify elevated blood pressure as Normal, Borderline, and Hypertension.

1.3 **Out of office BP measurements** are recommended to confirm the diagnosis of hypertension, with ambulatory blood pressure monitoring (ABPM) as the preferred method, and home blood pressure monitoring (HBPM) as an acceptable alternative.

In a joint position statement of the Philippine Heart Association (PHA) and the Philippine Society of Hypertension (PSH)[4], we are recommending a simplified blood pressure classification (Table 3) as recommended by guidelines for hypertension[5,6].

Table 1. Blood Pressure Classification for Adult Filipinos with Hypertension

Classification	Blood Pressure
Normal BP	< 120/80 mmHg
Borderline BP	120-130/ 80-90 mmHg
Hypertension	≥ 140/90 mmHg

Observational studies have shown that for every 10 mmHg increase in the blood pressure from 115/75mmHg, there is doubling of cardiovascular risk[7,8], thus, the rationale of setting the BP of < 120/80mmHg as the optimal level at which cardiovascular risk is set at the minimum. Several guidelines have defined normal or optimal BP at the level of < 120/80 mmHg. However, there are guidelines, such as International Society of Hypertension[9] and Singaporean Clinical Practice Guidelines (CPG)[10], that defined normal BP to be <130/85. The Korean CPG[11] has defined normal

BP <130/80 and Indian CPG[12] distinguished between a normal BP (<130/85) and an optimal BP (<120/80).

Most guidelines include a prehypertensive level, or a category of elevated BP that a significant number of previously categorized normal to high normal BPs eventually develop definite hypertension[13]. We recognize the need to alert patient and physician on this BP level for a significant impact on primary prevention is recognized, thus, the term borderline BP is used to describe BP 120-130/80-90 mmHg. Unfortunately, our physicians still use the aneroid sphygmomanometer, whose accuracy is compromised by the lack of calibration and constant maintenance check, because of cost over the preferred validated oscillometric device. In the setting where BP measurement is less than ideal, the potential for misdiagnosis or overdiagnosis may be real, hence the term borderline.

All international guidelines[6-12] , except the AHA/ACC guidelines[5] , define hypertension as a BP level of ≥ 140/90 mmHg. Most of the guidelines included in this analysis preferred to have different stages of hypertension. For practical reasons, a cut-off value was set by this guideline to simplify the diagnosis of hypertension and the treatment decisions surrounding it. This remains unchanged from the 2011 position paper that defined hypertension as any individuals with a blood pressure of ≥ 140/90mmHg[4]. The use of ≥140/90 mmHg as the cut-off for hypertension has shown in local prevalence studies that the prevalence rate was noted to be 35.1%[2] and 28%[1]. We felt that keeping the same standard of measurement used in the local prevalence studies would avoid confusion in local disease surveillance studies.

We recommend that blood pressure measurement should be in strict accordance with the proper standard, as recommended by the ACC/AHA guidelines[5]. The level of BP of ≥ 140/90 mmHg is determined at which the benefit of pharmacologic treatment supported by lifestyle interventions outweigh the risks/costs of treatment.

Clinical Question 2. Among adult Filipinos, what device is recommended for accurate blood pressure determination and monitoring?

Statements:

2.1 A properly validated semi-automated oscillometric sphygmomanometer (digital device) is recommended for in-office or out-of-office use.

2.2 The aneroid sphygmomanometer (manual device) may be used in-office or out-of-office provided the examiner is efficient and well trained, and the device is periodically checked according to standard maintenance procedures.

2.3 The aneroid sphygmomanometer is recommended for special cases like the presence of arrhythmias or extremes in BP levels.

The automated oscillometric device has now been recognized as the recommended gadget to use in measuring BP[15]. The device eliminates the need for familiarization with the Korotkoff sounds, the physical limitation in hearing, and the need for frequent calibration. However, there are issues with the use of the automated device. It may not be used in patients with atrial fibrillation because of the inconsistency in the oscillometric waveform. Production issues with different manufacturers may develop as they may utilize different algorithms to estimate mean arterial pressures (MAP), systolic BP (SBP), and diastolic BP (DBP). Thus, validation should be done on the product to ensure efficiency and to deal with accuracy issues[15,16]. The Philippine Society of Hypertension has validated automated machines in measuring BP among Filipino hypertensives[17].

The use of aneroid sphygmomanometers is subject to procedure and patient-related inaccuracies; thus, it was not recommended to be used in BP measurement[18]. However, in low-income countries such as the Philippines where oscillometric devices are not available, the use of aneroid sphygmomanometers may be used as an alternative as long as it is properly maintained and calibrated every six months. The mercurial sphygmomanometer is already phased out because of environmental concerns.

<u>Proper Blood Pressure Measurement[5]</u>

- The patient should be relaxed and rested >5min, in a sitting position, feet flat on the floor, back supported.
- No coffee, smoking, or exercise in the last 30 minutes.
- Urinary bladder should be emptied.
- No talking for both the patient and observer.
- The patient's arm should be resting on a desk.
- Check BP on both arms and use the arm with the higher BP on subsequent BP determination.
- The cuff should be of correct size, placed snug over the upper arm that is preferably without sleeves, with its middle portion at the level of the heart. It should cover 40% of the

upper arm and 80% of the arm circumference (standard bladder for adults is 13 cm wide, 22-24 cm long).

- When using a manual device, cuff deflation should be done at 2 mmHg/sec.
- Ideally, the systolic pressure should be estimated initially by the pulse obliteration upon inflation. Actual auscultatory determination is then done by inflating the cuff 20-30 mmHg above this palpated estimate.
- For auscultatory determination, use the fifth Korotkoff sound to determine the diastolic BP.
- Use an average ≥ 2 readings obtained on ≥ 2 occasions as an estimate of the BP level.
- The interval between BP measurements should be 1-2 min apart.

Use of Home BP (HBPM) and Ambulatory Blood Pressure (ABPM) in Diagnosing Hypertension

There is a growing number of studies focused on the usefulness of out of office BP monitoring in the diagnosis of hypertension. The evidence tends to favor the use of ABPM over office blood pressure[19]. In a meta-analysis of 24 studies based on confirmation by ABPM and HBPM over office-based diagnosis of elevated BP and its relationship with CVD risk, out of office BP is more correlated with vascular events, especially the ABPM[20]. It is recommended in this study that ABPM is the best method to use in BP measurement, with HBPM as an acceptable alternative[21]. ABPM was also shown as an important tool in diagnosing white coat hypertension (defined as having elevated office or clinic BP but having normal BP at home) based on a normal daytime ABP and elevated office BP. White coat hypertensive patients were shown to have a lower baseline cardiovascular risk[22].

Table 2. Differences Between ABPM and HBPM[6]

ABPM	HBPM
Measures BP over 24-hour period	Measures BP every day for several days
Measures BP during waking and sleeping hours	Measures BP during waking hours only
Measures BP during regular activities and sleep	Measures BP during rest in seated position
Measurements obtained automatically by device	Measurements triggered by patient
Patient unaware of BP readings	Patient usually aware of BP readings

ABPM is generally accepted as the better out of office BP measure (26) and is recommended here as the preferred mode of measure. ABPM is the primary method to detect nocturnal hypertension, to identify the extent of nocturnal dipping, to identify the early morning BP surge

pattern and estimating BP variability[20]. ABPM may be requested as a further confirmatory measure when there is still a need to strengthen diagnosis during telehealth consultation.

Studies using HBPM in measuring BP has shown that elevated HBPM readings are closely correlated to the development of target end organ damage, particularly that of left ventricular hypertrophy[23,24]. Home BP readings can also be used to monitor BP control. In an RCT comparing patients HBPM vs standard of care, more patients have BP control when they monitor at home compared to patients who receive usual care[25].

Indications for Out of Office BP Measurement

- ABPM or HBPM is recommended to confirm diagnosis of hypertension when office BP fluctuates around 140/90 mm Hg.
- ABPM or HBPM is recommended to establish the diagnosis of white coat and masked hypertension defined as having a normal office or clinic BP but with elevated blood pressures at home or out of office
- ABPM or HBPM is recommended to establish the diagnosis of resistant hypertension
- ABPM or HBPM is recommended to monitor efficacy of medications and BP control.
- ABPM is recommended when nocturnal hypertension is suspected or there is target organ damage in the presence of normal BP.
- ABPM is recommended for evaluation of postural, post-prandial, drug-induced hypotension, or hypotension from autonomic dysfunction.
- HBPM is recommended for use in telehealth consultation for diagnosis of hypertension.

Table 3. Definition of Hypertension According to Office, ABPM and HBPM Levels[6]

Type of Measurement	Blood Pressure Level
Office BP	≥ 140/90 mmHg
Ambulatory BP	
Mean Daytime BP (awake)	≥ 135/85 mmHg
Mean Nighttime BP (asleep)	≥ 120/70 mmHg
Mean 24-hour BP	≥130/80 mmHg
Home BP	≥135/85 mmHg

Clinical Question 3. Among adult Filipinos, what are the blood pressure targets among adult hypertensive Filipinos for the prevention of cardiovascular disease?

Statements:

3.1 A therapeutic threshold of greater than or equal to 140/90 mmHg to achieve a goal of less than 130/80 is recommended for all patients with hypertension.

3.2 For the very elderly, defined as 80 years old and above, a therapeutic threshold of greater than or equal to 150/90 to achieve a goal BP of less than 140/90 is recommended

All guidelines agree that patients with hypertension should receive anti-hypertensive treatment on top of diet and lifestyle modification to reduce blood pressure to treatment targets. Lowering blood pressure to less than 140/90 has been shown repeatedly to reduce morbidity and mortality[6-7,26-27].

There has been extensive discussion on lowering the target BP to <130/80 as a result of the SPRINT trial. SPRINT compared two different treatment targets <140/90 vs <120/80 among patients with high cardiovascular risks excluding patients with diabetes or previous stroke[28]. The study showed that intensive lowering of blood pressure was associated with 25% reduction in major CV events and 27% reduction in all-cause mortality but no significant reduction in stroke and MI[28] which favors more intensive treatment targets for patients with higher CV risks.

An updated meta-analysis that included SPRINT looking at cardiovascular effects of more vs. less intense BP treatment levels showed that more intense BP lowering reduced the risk of stroke (RR: 0.71; 0.60-0.84), coronary events (RR: 0.80; 0.68-0.85), major CV events (RR: 0.85; 0.68-0.85) and CV mortality (RR: 0.79; 0.63-0.97) but not heart failure and all-cause death[6]. When the RCTs were stratified according to the three different BP cut offs (SBP 150,140 and 130 mmHg), it showed that a 10/5 mmHg decrease in SBP/DBP across each BP cut off level significantly reduced the relative risk of all outcomes, but the absolute risk reduction tends to decrease significantly at lower BP cut offs[29-30].

Some guidelines [6,9] have recommended not to lower BP to less than 120 due to increased risk of adverse events, a decrease in incremental benefit of BP lowering on CV events and mortality as the target BP was lowered,[29-30] and discontinuation of treatment because of treatment related adverse effects in patients with lower BP values[10]. Based on the available evidence, it is prudent

to lower office BP to a target of less than 130/80 mmHg if well tolerated. However, it should not be lowered than office SBP of 120mmHg especially for older individuals, higher risk patients with co morbidities and CVD where the risks outweigh the benefits[31].

It is important that risk-factor identification to risk-stratify hypertensive patients is done since the presence of one or more additional CV factors increases the risk of coronary, cerebrovascular, and renal diseases in hypertensive patients. The risk factors were identified in the 2020 Dyslipidemia Philippines CPG as male sex, postmenopausal women, smoker, hypertension, BMI > 25 kg/m^2 , family history of premature coronary artery disease, proteinuria and left ventricular hypertrophy. Individuals with low risk have 1-2 identified risk factors, while high risk individuals have three or more risk factors[32].

A review of the 15 guidelines[15-11, 33-41] showed that BP should be lowered to less than 140/90 with 9 out of the 15 setting the target to less 140/90 and 5 guidelines recommending a target of 130/90 or less.

This local guideline will take a practical approach to BP targets in recommending a **threshold of greater than or equal to 140/90 mmHg to start therapy**. This can be addressed with diet and lifestyle modifications alone in low-risk hypertensives or concomitant lifestyle changes with medical treatment in high-risk individuals. We recommend these interventions to achieve a blood pressure of < 130/80 mmHg in Filipino hypertensive individuals.

It is important that risk-factor identification to risk-stratify hypertensive patients is done since the presence of one or more additional CV factors increases the risk of coronary, cerebrovascular, and renal diseases in hypertensive patients.

For the very elderly defined as 80 years old and above in 11 guidelines, 5 out of 11 recommended a slightly higher target BP of less than 150/90, while 5 out of 11 recommending a target of 140/90.

Physical Examination for Hypertensive Individuals

A complete history and physical examination are warranted and can provide the physician clinical clues in diagnosing hypertension and identification of Hypertension-mediated organ damage (HMOD). It can also help in detecting secondary forms of hypertension. Physical examination

should include checking for pulse rate and rhythm, the jugular venous pressure, apex beat and extra cardiac sounds. It is also important to check for carotid, abdominal and femoral bruits, radio-femoral delays, and peripheral edema. The physician can also look for other signs of secondary causes of hypertension such as increased body mass index, increased waist circumference, fatty deposits, abdominal striae, enlarged neck circumference, enlarged thyroid glands, and enlarged kidneys.[9]

Laboratory Investigations for Hypertensive Individuals

The physician can order the following diagnostic test to assess and confirm suspicion of HMOD, coexistent diseases, or secondary hypertension. These would include complete blood count, serum electrolytes sodium, potassium, creatinine and blood urea nitrogen to estimate glomerular filtration rate. It is also recommended to check for fasting glucose and lipid profile. To check for albuminuria, it is recommended to do a dipstick urinalysis, or if available, urine micral test, spot or 24-hour urine albumin-creatinine ratio. To check for left ventricular hypertrophy 12L ECG or echocardiography can be done. For cardiac dysfunction, atrial dilation or aortic coarctation, an echocardiography is recommended. A carotid ultrasound is requested to check for atherosclerosis or stenosis. A simple fundoscopy can be utilized to check for retinal changes, hemorrhages, and papilledema. Additional tests can be done to check for other HMOD or secondary causes such as a cranial CT/MRI, ankle-brachial index, serum uric acid, thyroid-stimulating hormone, aldosterone-renin ratio, serum and urinary metanephrines, salivary or serum cortisol, and liver function tests[5,9].

Clinical Question 4. Among adult Filipinos with hypertension, what are the available treatment options?

Clinical Question 4.1. What non-pharmacologic therapy is recommended for adults with hypertension?

Statements

4.1 Lifestyle modifications remain cornerstone in the management of hypertension. Robust clinical trial evidence has shown that it can prevent or delay the onset of high BP and can

reduce cardiovascular risk. Healthy lifestyle choices are the first line of antihypertensive treatment. Modifications in lifestyle can also enrich the effects of antihypertensive treatment. Lifestyle modifications should include the following:

4.1.1. Sodium restriction to as low as 1500 mg/day
4.1.2. Dietary Approaches to Stop Hypertension (DASH) meal plan
4.1.3. Aerobic physical activity and (dynamic) resistance exercises
4.1.4. Abstinence from alcohol or moderate alcohol intake
4.1.5. Significant weight loss of $\geq$ 5% of the baseline weight
4.1.6. Smoking cessation

Effective cardiovascular protection for hypertensive patients requires achievement of blood pressure targets with appropriate lifestyle measures and anti-hypertensive medications. The goal of treatment strategies is to reduce excess cardiovascular morbidity and mortality from chronically elevated blood pressure. The recommendations from the different guidelines are similar to the local recommendations.

Effective lifestyle modifications may delay or prevent the need for drug therapy in new-onset, low-risk hypertensives. The benefit of these healthy choices should be sustained over a significant period to continue to confer advantage. Lifestyle measures that have been shown to reduce BP are sodium restriction, the DASH diet, increased physical activity, abstinence of alcohol consumption, maintaining an ideal body weight and smoking cessation[5-6,9].

Sodium restriction[42-43] is recommended for all patients with hypertension. The AHA[5] recommends that sodium intake be limited to 2300 mg/d (about roughly half a teaspoon of table salt) in most healthy individuals and 1500 mg/d in people with prehypertension or hypertension. Simply counseling individuals to reduce sodium intake leads to a reduction in BP by 3 to 4/1 to 2 mm Hg, empowering health care providers to talk about dietary sodium in their daily practice[7]. Providers should remind their patients that adding salt to the food on their plate contributes only a small amount to their daily sodium intake so patients should be advised to avoid condiments, fish sauce (patis), soy sauce, shrimp paste (bagoong) or even catsup and tomato sauce. Even more sodium is intrinsically part of many prepared foods and conservation processes (e.g., cup noodles, canned foods and soups). Sodium is found in high amounts in many foods, including pizza, tacos, burgers, sandwiches, soups, and pasta dishes, as well as meat, poultry, seafood, condiments, and sauces.

The Dietary Approaches to Stop Hypertension (DASH) meal plan[44-45], which is low in sodium and high in dietary potassium, can be recommended for all patients with hypertension without renal insufficiency[28-31]. The DASH diet is rich in fruits, vegetables, low-fat dairy, fish, whole grains, fiber, potassium, and other minerals at recommended levels and low in red and processed meat, sugar sweetened foods and drinks, saturated fat, cholesterol, and sodium. The US Department of Agriculture review concluded that a DASH diet lowers systolic BP by 5 to 6 mm Hg and diastolic BP by 3mmHg compared with a typical American diet, benefiting both men and women, independently of age, race, and hypertensive status[7,28-31].

Aerobic physical activity and exercises reduce blood pressure by around 8.3/5.2 mm Hg[20] with the benefit being greatest for those who are sedentary. Exercise regimens effective for lowering BP lasted at least 12 weeks, were moderate to vigorous-intensity aerobic exercises done 3-4x/week, lasting on average for 40 minute per session. More recent data also show that that aerobic and dynamic resistance exercise may be equally effective in reducing BP at a lower volume of physical activity[46].

Abstinence from alcohol intake is recommended among Filipinos due to a high prevalence of binge drinking, although numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality[10,37].

Significant weight loss of $\geq$ 5% of the baseline weight through a combination of dietary modification, exercise and physical activity can directly improve BP in hypertensives[46]. In overweight and obese hypertensive patients, weight loss should be encouraged. According to the WHO Asian Classification, overweight is defined as BMI from 23.0 kg/m2 to less than 25.0 kg/m^2 , while obesity is defined as BMI 25.0 kg/m2 or above. In a meta-analysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively[46]. Both overweight and obesity are associated with an increased risk of CV death and all-cause mortality.

Finally, persons with hypertension should be strongly counseled about **smoking cessation** for overall cardiovascular risk reduction. Studies using ABPM have shown that both normotensive subjects and untreated hypertensive smokers present higher daily BP values than non-smokers[9].

Clinical Question 4.2. What are the preferred drugs for the treatment of hypertension among adult Filipinos for the prevention of cardiovascular diseases?

Statements:

4.2.1 Among persons with **uncomplicated hypertension**, defined as sustained BP ≥ 140/90 with no associated HMOD, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers, thiazide/thiazide-like diuretics are all suitable first-line antihypertensive drugs, either as monotherapy or combination.

4.2.2 Ideal combination therapy includes renin-angiotensin-system (RAS) blocker with calcium channel-blocker (CCB) or thiazide/thiazide-like diuretics**.** Other combinations of the five major classes (including beta blockers) may also be used in patients with compelling indications for the use of specific drug classes.

4.2.3 ACE inhibitors & ARBs are not recommended to be used in combination. Likewise, combinations of ACE-I or ARBs with direct renin inhibitors should not be used.

4.2.4 The use of free combinations is recommended if single-pill combination therapy is not available or not affordable.

4.2.5 Beta blockers are suitable as initial therapy in hypertensive patients with coronary artery disease, acute coronary syndrome, high sympathetic drive, and pregnant women. We prefer the newer generation beta blockers for those with congestive heart failure such as bisoprolol, carvedilol, metoprolol succinate or nebivolol.

4.2.6 Among patients with BP >150/100 mm Hg (or >160/100 mm Hg in the elderly), a combination of 2 agents, preferably combination of a RAAS inhibitor (ARB/ACE-is) and CCB or diuretic, should be given initially since it is unlikely that any single agent would be sufficient to achieve the BP target.

Therapeutic strategies must include lifestyle changes, effective treatment of the other risk factors and aggressive BP control to reach target levels to reduce the residual cardiovascular risk. Drug treatment is recommended in patients with uncomplicated hypertension despite lifestyle modification for 3 months, or with elevated BP with HMOD is already present. In patients with high-risk hypertension fulfilling any one of these criteria as given below and in the next paragraphs:

1. Presence of three or more risk factors (≥3 risk factors)
2. Presence of HMOD
3. Presence of Disease

Drug treatment should also be initiated simultaneously with lifestyle interventions[5,6].

Risk factors: Age (>65 years), sex (male>female), heart rate (>80 beats/min), increased body weight, diabetes, high LDL-C/triglyceride, family history of CVD, family history of hypertension, early-onset menopause, smoking habits, psychosocial or socioeconomic factors[32].

Hypertension-mediated Organ Damage (**HMOD):** LVH (LVH with ECG), moderate-severe CKD (CKD; eGFR <60 ml/min/1.73m^2), any other available measure of organ damage.

Significant Comorbid Diseases which increase cardiovascular risk with the background of hypertension: previous coronary heart disease (CHD), HF, stroke, DM, peripheral vascular disease, atrial fibrillation, CKD grade 3+

In the Presyon 3 Data[1], a survey looking at the prevalence of hypertension in the Philippines, 75% of Filipino hypertensives are medically treated but only 20% are controlled or reaching target BP levels. Pharmacologic treatment strategies thus play a big role in optimizing management. The recommendations given in this local guideline for medical treatment options mirror those made by the latest European and American guidelines[5-6].

Based on evidence on prognosis improvement from large-scale clinical studies ACE inhibitors, ARBs, CCBs, diuretics and beta-blockers are selected as first-line drugs[20,29-30]. Overall, major CV outcomes and mortality were similar with treatment based on initial therapy with all five major classes of treatment. Compelling indications and contraindications dictate preferential use of each class of drugs[18,23]. We recommend the longer-acting ARBs as well ACE inhibitors such as telmisartan, olmesartan and irbesartan, perindopril because it can be given once-a-day.
ACE inhibitors and ARBs have similar evidence on major CV events and mortality outcomes[20,23,24]. They reduce albuminuria more than other BP-lowering drugs[22], are effective in regressing HMOD, such as LVH and have been found to reduce incident AF[20]. However, they should not be combined for lack of benefit on outcomes and an excess of renal adverse events[25,26]. ARBs have lower treatment discontinuation rates for adverse events compared to all other antihypertensive therapies[27].

CCBs have comparable effectiveness as other major drug classes on BP, major CV events, and mortality outcomes[23, 28]. They have a significant effect on stroke reduction, are more effective than

beta-blockers in slowing carotid atherosclerosis and in reducing LVH and proteinuria[25], but are less effective at preventing HFrEF. [28,] Dihydropyridines (especially amlodipine) have been well studied in clinical trials showing benefit for outcomes with smaller studies using nondihydropyridines (verapamil and diltiazem)[29].

Diuretics, especially the thiazide-like diuretics (chlorthalidone and indapamide), have been effective in preventing CV morbidity and mortality in patients with hypertension with a benefit for heart failure management[29]. Both thiazides and thiazide-like agents are less effective antihypertensive agents in patients with a reduced GFR (eGFR <45 mL/min). Loop diuretics such as furosemide (or torsemide) should be used for its BP lowering effect when the eGFR is <30 mL/min.

Robust clinical trial evidence have shown that beta-blockers significantly reduce the risk of stroke, heart failure, and major CV events in hypertensive patients with less efficacy for stroke prevention and regressing LVH compared to other drug classes[17, 18, 21,23]. They are preferred for symptomatic angina, heart rate control, post-myocardial infarction, HFrEF, and for women of reproductive age[17,18]. Vasodilating beta-blockers (labetalol, nebivolol and carvedilol) have more favorable effects on endothelial functions with lesser side effect profiles than classical beta-blockers[30,31]. Beta-blockers, as well as diuretics, especially in combination, are associated with increased risk of new-onset diabetes in patients with metabolic syndrome[31].

All five major first-line drug classes can be combined with one another except for ACE inhibitors and ARBs. Combination ACE inhibitors or ARBs with either a CCB or thiazide/thiazide-like diuretic are complementary because both CCBs or diuretics activate the RAS and will also limit adverse effects associated with diuretic or CCB monotherapy. The choice for starting on initial combination therapy results in greater achievement of BP lowering at the shortest amount of time. Low-dose combination therapy has been shown to be more effective than maximal dose monotherapy[32].

Additional classes of drugs are known to be associated with a higher risk of adverse effects [e.g. alpha-blockers, centrally acting agents, and mineralocorticoid receptor antagonists (MRAs)] with lesser evidence for cardiovascular risk reduction. However, these are useful additions to patients whose BP cannot be controlled by proven combinations of the first-line major drug classes.

Follow up for Newly Diagnosed Hypertensive Individuals

This CPG recommends that newly diagnosed hypertensive individuals who have started on antihypertensive medications be followed up after one (1) month. However, we recommend a closer follow-up and monitoring (2-3 weeks) for patients who have exceptionally elevated readings (eg: ≥ 160/100mmHg)[5,6].

Table 4. Antihypertensive Medications Available in the Philippines (2020)

Anti-Hypertensive Drugs	Available Dose Formulations	Dosing
Diuretics		
Hydrocholorothiazide (HCTZ)	25mg, 50mg	Once daily
Indapamide	1.25mg, 2.5mg, 5mg	Once daily
Furosemide	10mg, 20mg, 40mg	Every 6 hours
Metolazone	5mg	Once daily
Spironolactone	25mg, 50mg	Once daily
Eplerenone	25mg, 50mg	Once daily
ACE inhibitors		
Captopril	25 mg, 50 mg	Twice daily
Enalapril	5 mg, 10 mg, 20 mg	Once to twice daily
Imidapril	5 mg, 10 mg,	Once daily
` Fosinopril	10 mg, 20 mg, 40 mg	Once daily
Perindopril	4 mg, 8 mg, 16 mg	Once daily
Quinapril	5mg, 10 mg, 20mg, 40mg	Once daily
Ramipril	5mg, 10mg	Once to twice daily
Angiotensin Receptor Blockers		
Candesartan	8mg, 16mg, 32mg	Once daily
Irbesartan	150mg, 300mg	Once daily
Losartan	50mg, 100mg	Once to twice daily
Olmesartan	20mg, 40mg	Once daily
Telmisartan	40mg, 80mg	Once daily
Valsartan	160mg, 320mg	Once to twice daily
Direct Renin Inhibitor		
Aliskiren	150mg, 300 mg	Once daily
Calcium Channel Blockers		
Amlodipine	5mg, 10mg	Once daily
Diltiazem	30mg,60mg,90mg,	Once to four times daily
Diltiazem SR	120mgSR,180mgSR	Once daily
Felodipine	2.5mg, 5mg, 10mg	Once daily
Isradipine	1.25mg,2.5mg, 5mg	Once daily
Nicardipine	10ml/vial	
Nifedipine	5mg, 10mg, 20mg, 30mg	Once to three times daily
Verapamil	40mg, 80mg,	Once to three times daily
Verapamil SR	180mg SR, 240mg SR	Once daily

Beta Blockers		
Atenolol	25 mg, 50 mg, 100 mg	Once to two times daily
Bisoprolol	5 mg, 10 mg	Once daily
Carvedilol	6.25 mg, 25 mg	Once to two times daily
Metoprolol tartrate	25 mg, 50 mg, 100 mg	Once to three times daily
Metoprolol succinate	25, 50, 100 mg	Once daily
Nebivolol	2.5 mg, 5 mg, 10 mg, 40 mg	Once daily
Propranolol	10 mg, 40 mg	Once to three times daily
Alpha Blockers		
Doxazosin	1mg, 4mg	Once daily
Prazosin	500 mcg	Once daily
Terazosin	1mg, 2mg, 5mg	Once daily
Central Agonists		
Methyldopa	250mg	Once to four times daily
Clonidine	75mcg	Once daily
Vasodilators		
Hydralazine	10mg	Once to three times daily

Table 5. Available Single-Pill Combinations (SPCs) in the Philippines

Fixed Dose Combinations	Available Doses
Beta blockers + Diuretics	
Bisoprolol + HCTZ	2.5/6.25 mg, 5/6.25mg, 10/6.25mg
Metoprolol + HCTZ	50/25mg, 100/25mg, 100/50mg
ACE Inhibitors + Diuretics	
Enalapril + HCTZ	20/12.5mg
Perindopril + Indapamide	5mg/1.25mg
ACE Inhibitors + Calcium Channel Blockers	
Perindopril + amlodipine	3.5/2.5mg, 5/5mg, 10/10mg
Angiotensin Receptor Blockers + Diuretics	
Candesartan + HCTZ	16/12.5mg, 32/12.5mg, 32/25mg
Irbesartan + HCTZ	150/12.5mg, 300/12.5mg, 300/25mg
Losartan + HCTZ	50/12.5mg, 100/12.5mg, 100/25mg
Olmesartan + HCTZ	20/12.5mg, 40/12.5mg, 20/25mg, 40/25mg
Telmisartan + HCTZ	40/12.5mg, 80/12.5mg, 80/25mg
Valsartan + HCTZ	80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg, 320/25mg
Angiotensin Receptor Blockers + CCBs	
Candesartan + amlodipine	8/5mg
Irbesartan + amlodipine	150/5mg, 300/5mg, 300/10mg
Losartan + amlodipine	50/5mg
Olmesartan + amlodipine	20/5mg, 20/5mg, 40/5mg, 40/10mg

Telmisartan + amlodipine Valsartan + amlodipine	40/5mg, 40/10mg, 80/5mg, 80/10mg 80/5mg, 160/5mg, 160/10mg
Direct Renin Inhibitor + Diuretic Aliskiren + HCTZ	150/12.5mg, 150/25mg, 300/12.5mg, 300/25mg
Beta blockers+Calcium channel blockers Atenolol + amlodipine	25/5mg, 50/5mg

* SPCs are given once daily

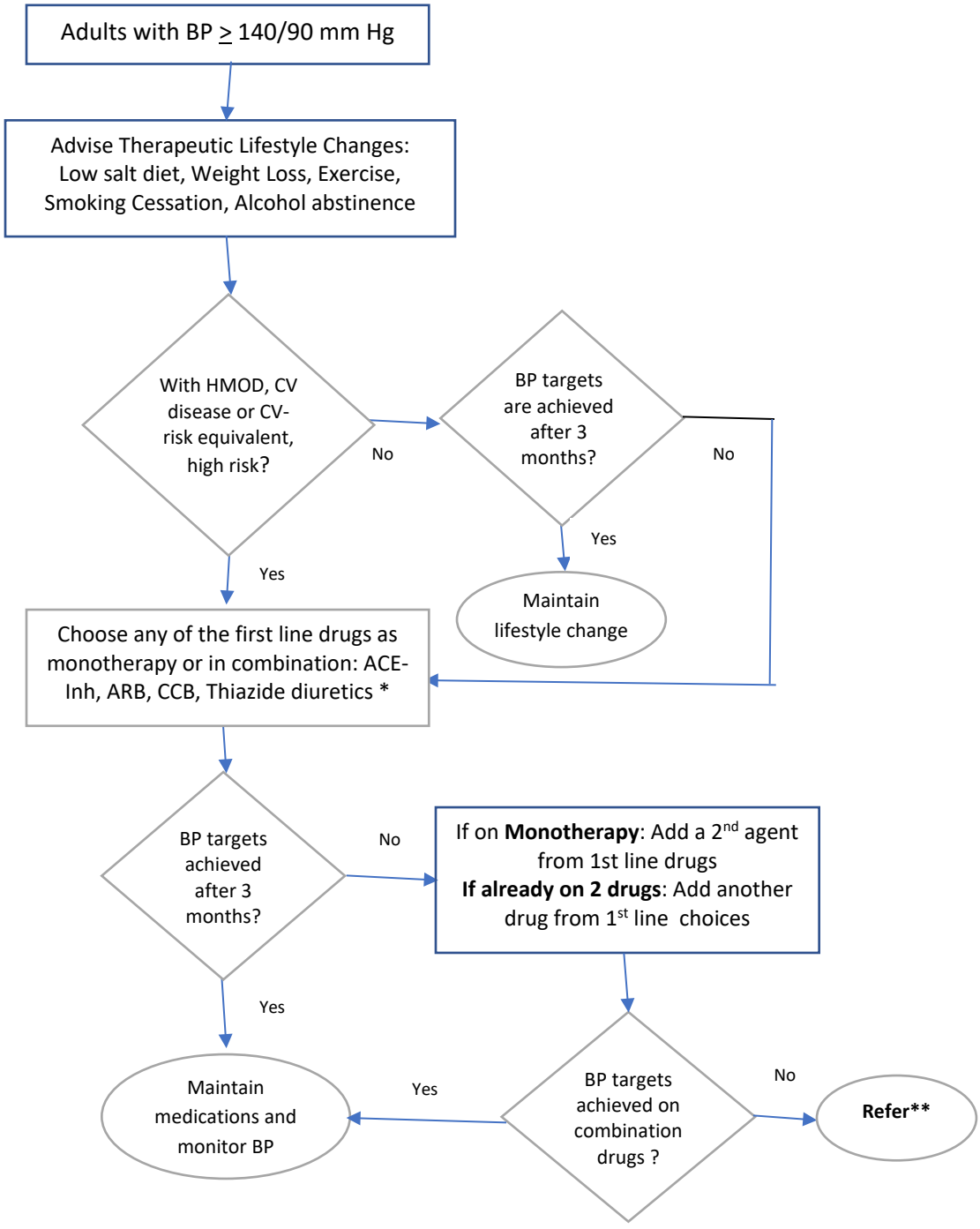


Figure 2. Algorithm for the Management of Hypertension among Adults

Resistant Hypertension

Resistant hypertension is defined as BP that remains above target despite the concurrent use of three or more antihypertensive medications of different classes, one of the agents should be a diuretic, and all the drugs that are prescribed are at maximum tolerated doses[5,6,8]. Individuals whose BP is controlled but are requiring four or more antihypertensive medications should also be considered resistant to treatment. In the PRESYON-3[1], 73% of those treated with anti-hypertensive medications have uncontrolled BP, and most of them are elderly. Treatment involves combination of three or more anti-hypertensive medications, including a diuretic. Adding aldosterone antagonists provide significant benefit with resistant hypertension. If the patient is still hypertensive, additional medications are added sequentially, and these may include vasodilating beta blockers, centrally acting agents, and vasodilators. It must be noted that a referral to a hypertension specialist is warranted if therapy has progressed to adding a fourth agent[5].

II. Blood Pressure Management in Persons with Diabetes Mellitus

Hypertension is an anticipated co-morbid condition that is found in majority of persons with established diabetes mellitus. In the DiabCare Philippines survey (2008), hypertension was found in nearly 70% of persons with established diabetes who were consulting general practitioners and diabetes specialists[47]. Majority of the patients in this study have had diabetes for 5 or more years. However, another local study among newly diagnosed diabetics (diabetes for 1 year or less), showed that 40% of the participants already have hypertension[48]. Similar to international cohorts, persons with diabetes in the Philippines, even the newly diagnosed, have a high prevalence of co-existing hypertension.

While poor glycemic control among persons with diabetes is strongly associated with the development of microvascular complications, hypertension as well as dyslipidemia are major determinants of macrovascular complications. Good control of blood sugar early in the course of the disease leads to a legacy effect of better cardiovascular outcomes in the long run after around ten or more years, but not early on. In contrast, control of hypertension leads to prevention of both types of complications (macro- and microangiopathy) both in the short and long term. So the rationale for controlling blood pressure well among persons with diabetes is not only to prevent early cardiac death or stroke, but also to prevent retinopathy, neuropathy and nephropathy[5, 49-52]

However, control of blood pressure among persons with diabetes is often difficult, requiring typically 2 or more medications in order to achieve targets. Hence, the debate about which medications to use among this population is no longer about which are the preferred drugs since many end up with combinations typically of the preferred initial therapy which are RAS blockers plus other calcium channel blockers, thiazide type diuretics and beta blockers.

Treatment of hypertension appears to confer greater benefits in people with diabetes than in age-matched people with hypertension who do not have diabetes. The benefits of intensive BP lowering may even exceed those of intensive glycemic control in people with diabetes mellitus for the prevention of CV complications.[50-51] Because cardiovascular disease (CVD) is the most common cause of death in people with diabetes mellitus[49] BP control is paramount.

Clinical Question 5. Among adult persons with diabetes, what is the threshold for (pharmacologic) treatment of elevated blood pressure?

Statement 5: Among persons with diabetes and hypertension, it is recommended that drug therapy (along with lifestyle advice) be initiated at a blood pressure of **140/90 mm Hg or higher.**

Most persons with type 2 diabetes and hypertension can be considered to belong to a high-risk CV category[5] and this appears true among the general population of persons with established Type 2 diabetes in the Philippines. The justification for this recommendation is the fact that both macrovascular and microvascular complications, as well as various cardiovascular risk factors (obesity, dyslipidemia) are prevalent among persons with diabetes. In the Diabcare Philippines 2008[47] data, 95% of all the participants had dyslipidemia and nearly 70% had hypertension. In this cohort of patients with established Type 2 diabetes, around 20% already had some form of nephropathy, 35% retinopathy (8% severe) and 15% already had a stroke, myocardial infarction or had undergone CABG or angioplasty or with overt CAD, and 75% had a BMI more than 23 kg/m^2.[47]

Such an observation is also seen among newly diagnosed adults with T2DM (mean age of 50 years) in the CANDI Manila[48] study which showed a high prevalence of diabetes complications. Electrocardiographic findings showed that 2% have evidence of myocardial infarctions, 3% had ischemic changes, and 6% had left ventricular hypertrophy. Hypertension was found in 42% of individuals with a mean BP of 144/88 mm Hg, and 80% of all subjects had LDL $\geq$ 100 mg/dL, with another 38% with elevated triglyceride $\geq$ 150 mg/dL.[52]

Of the 12 guidelines that were examined, 5 did not give any recommendations regarding the threshold for starting pharmacologic therapy. 5 guidelines gave a threshold of 140/90 mm Hg[6, 9, 35, 40, 53] or higher for starting drug therapy, while 2 gave a recommendation of 130/80 mm Hg or higher as the cut-off blood pressure for intervention. These are the guidelines of ACC /AHA[5] and the US Endocrine Society[54], although the latter also gave a condition that if the 10-year risk for CV events is more than 10%, then pharmacologic therapy should be given at a BP of 130/80 mm Hg and higher, while those with less 10% ASCVD risk should be advised on lifestyle modification. Consistent then with the section on general guidelines for treatment, plus the recommendations of majority of the guidelines, the threshold for treatment continues to be 140/90 mm Hg.

Clinical Question 6: Among adults with diabetes and hypertension, what non-pharmacologic therapy is recommended?

Statement 6: The general advice for non-pharmacologic therapy among persons with diabetes is similar to the general population with hypertension as follow (Refer to section of General Management of Hypertension):

6.1 Sodium restriction to as low as 1500 mg/day
6.2 Dietary Approaches to Stop Hypertension (DASH) meal plan,
6.3 Aerobic physical activity and (dynamic) resistance exercises
6.4 Abstinence from alcohol or moderate alcohol intake
6.5 Significant weight loss of $\geq$ 5% of the baseline weight
6.6 Smoking cessation

Among persons with diabetes and hypertension, screening for obstructive sleep apnea may be warranted as randomized studies of people with diabetes have shown that treatment of OSA (by CPAP) reduces blood pressure.

Clinical Question 7. Among adults with diabetes and hypertension, what are the blood pressure targets for prevention of cardiovascular diseases (mortality and morbidity)?

Statement 7: A blood pressure target of <130/80 mm Hg is recommended for most persons with diabetes mellitus and hypertension; however, do not lower down the blood pressure below 120/70 due to an increased risk for cardiovascular events.

While cardiovascular risk reduction (myocardial infarction, CV death) is already significant for BP < 140/90 mm Hg (with no additional benefit for < 120 mm Hg), a lower blood pressure target has additional benefit for stroke reduction and decreased risk for nephropathy. However, there is also a recommendation not to lower the BP to less than 120/70 mm Hg due to increased risk for adverse cardiovascular outcomes.

Although proportional associations of BP lowering treatment for most CV outcomes studied were attenuated below a systolic BP level of 140mmHg, data indicate that further reduction below 130 mmHg is associated with a lower risk of stroke, retinopathy, and albuminuria, potentially leading to net benefits for many individuals at high risk for those outcomes[55]. In the past, the recommendation to lower systolic BP to <130 mmHg had been partly based on prospective cohort data; specifically, the Pittsburgh Epidemiology of Diabetes Complications Study[57] (in people with type 1 diabetes mellitus) and the UKPDS[50] (in people with type 2 diabetes). These studies demonstrated a linear relationship between systolic BP levels and mortality, CAD, overt diabetic nephropathy and proliferative retinopathy[56,57]. These associations were maintained even after adjustment for other confounding factors (such as lipid levels, age, sex and glycemic control). In these studies, direct relationships were seen between the magnitude of BP reduction and reductions in risk of hypertension-related complications, over time.

This target was challenged in the ACCORD BP study arm which showed that a blood pressure of < 140 mm Hg did not differ to a BP < 120 in terms of CV risk reduction; however, the same study showed that there is still substantial stroke reduction with lower systolic BP[58]. The meta-analyses of Bangalore et al also showed that while the other components of major adverse cardiac events were not improved, lowering BP <130 mmHg conferred additional protection against stroke [55, 59-61]. Lowering diastolic BP to equal to or less than 80 mm Hg is also supported by the HOT trial where 1,500 persons with diabetes among 18,790 participants were included. In the over-all trial, there was no cardiovascular benefit with more intensive targets but in the subpopulation with diabetes, an intensive diastolic BP target of less than or equal to 80 mm Hg showed significantly reduced risk (51%) of CVD events[62]

However, there is also a recommendation not to lower the BP to less than 120/70 mm Hg due to increased risk of adverse cardiovascular outcomes[63]

A review of the 12 guidelines[5-6,9-12,32-40,64] show that 9 out of the 12 have set the target to be < 130/80 mm Hg while the rest recommend a slightly higher number. Two of the guidelines set a different target for the elderly; the UK NICE[40] sets a target of below 135/85 mmHg for adults aged under 80, and below 145/85 mmHg for adults aged 80 and over, while the ACC/AHA[5] states that in older people aged ≥ 65 years old, the target SBP range of 130-139 mm Hg. Data from ACCORD has also been the basis for the recommendation not to lower the BP to less than 120/70 mm Hg due to increased risk of adverse cardiovascular outcomes.

Clinical Question 8. Among adults with diabetes, what are the preferred drugs for the treatment of hypertension?

Statements:

8.1. It is recommended to initiate treatment with a low-dose combination of a RAAS blocker (ACE-I or ARB) with a CCB or thiazide/thiazide-like diuretic, preferably using a single-pill combination (SPC). Free tablet combinations may also be given if SPCs are not available.

8.2. The combination of ACE and ARB is not recommended due to a higher risk of hyperkalemia and renal failure.

Consistent with the concept that majority of persons with established diabetes are already of high CV risk, and as well are at high risk to develop microangiopathy especially nephropathy, RAAS based therapies (ACE-inhibitor and Angiotensin-2 receptor blockers) are the drugs of choice as base drugs for persons with diabetes who have hypertension. The guidelines of the Canadian Diabetes Association[38] specifically identify those people with diabetes, and those people with evidence of increased urinary albumin excretion, as persons at high risk for CV events. Their recommendations also recognize those people with known CVD, renal disease or elevated urinary albumin excretion, as well as those people with additional CV risk factors to be high-risk people who should receive an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy.

The use of combination therapy of a RAS blocker with a CCB or thiazide/thiazide-like diuretics is advocated by at least 4 of the reviewed guidelines [6,9,35,39,55], and that treatment can be further escalated according to their recommended treatment algorithms[55,65-66]. However, multiple drug therapy is generally required to achieve blood pressure targets among persons with diabetes (PWD). As much as 90% of PWDs with hypertension require three anti-hypertensive medication

to achieve target.[67]These drugs may be used as add-on therapy if BP targets are not reached: diuretics, calcium channel blockers (CCBs), beta blockers and peripheral alpha blockers. However, an ARB plus ACEI combination more than doubles the risk of renal failure and hyperkalemia and is therefore not recommended.[68-69] While initial combination therapy is advocated by these 4 guidelines, the AACE is slightly different in that it recommends combination therapy only among those with an initial BP >150/100 mm Hg since monotherapy is unlikely to be sufficient to reach BP targets. The ADA likewise recommends combination therapy among those with BP $\geq$ 160/100 mm Hg.

As already stated in the general guidelines, the choice for starting on initial combination therapy results in greater achievement of BP lowering at the shortest amount of time. Low-dose combination therapy has been shown to be more effective than maximal dose monotherapy in the general population of persons with hypertension[70], more recent meta-analysis has also shown it specific effects on persons with diabetes. In a 2015 network meta-analysis of 27 studies with nearly 50,000 participants, it was seen that there was no benefit of any single antihypertensive class in the reduction of mortality in hypertensive persons with type 2 diabetes. Reduction of cardiovascular mortality was only observed among patients treated with ACE-inhibitors and CCB combination, which may be related to lower blood pressure levels.[71] Combination therapy between an ARB and another drug class was not included in this network meta-analysis.

The other clinical trial that supports the use of combination therapy, but which was not included in the previous meta-analysis is the ADVANCE trial. The BP-lowering arm of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial used the ACE-inhibitor perindopril combined with indapamide as a single pill combination, resulting not only to decreased CV outcomes (death from CVD was reduced by 18%) but also with significant impact on microvascular outcomes including nephropathy and retinopathy. The six-year observational study called ADVANCE-ON still found significant reduction in risk of death although already attenuated. The achieved blood pressure in the intervention group was 136/73 mmHg.[72-73]

The clinical trial called ACCOMPLISH, while included in the meta-analysis is worthy to mention because like ADVANCE, it supports the use of two single-pill combination therapy. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial enrolled participants at high risk of cardiovascular events

(60% with diabetes) and demonstrated a decrease in morbidity and mortality with the ACE inhibitor benazepril plus the dihydropyridine CCB amlodipine versus benazepril and the thiazide-like diuretic hydrochlorothiazide [74-75].

While more trials are needed to support the use of single pill combinations for the initial therapy of hypertension among persons with diabetes, there is already enough data to support the use of initial combination therapy of ACE-inhibitors or ARB with CCB compared to monotherapy, or alternatively ACE-I/ARB with thiazide or thiazide-like diuretic as supported by the ADVANCE trial[72].

III. Blood Pressure Management in Persons with Chronic Kidney Disease

The number of people afflicted with kidney problems have been increasing, and two of the main causes of chronic kidney disease are diabetes mellitus and hypertension. Diabetic nephropathy is now the leading cause of end stage renal disease in the developing world approximating 50% of the cases[76]. Locally, diabetes has surpassed glomerulonephritis as the leading cause of chronic renal failure. Together with hypertension, diabetes accounts for almost 60% of dialysis patients[77]. Hypertension is also highly prevalent in individuals with chronic kidney disease. The prevalence of hypertension increases from 36% in stage 1 to 84% in chronic kidney disease stage 4 and 5[78]. Blood pressure control is fundamental to the care of patients with chronic kidney disease and is relevant at all stages of chronic kidney disease regardless of underlying cause.

With diabetes and hypertension as the two most common cause of CKD, most of the adopted guideline and recommendation were obtained from groups dealing with these two important risk factors for CKD. To date, the most quoted guidelines remain to be from the Kidney Disease Improving Global Outcomes (KDIGO)[78] guidelines, an update of the previous work of Kidney Disease Outcome Quality Initiative (KDOQI)[79]. The most recent guideline at present available for clinicians handling hypertension among diabetic patients with chronic kidney disease and takes greatest advantage of the most recent studies to date at its disposal is the American Diabetes Association Standards of Medical Care in Diabetes – 2019[53].

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health. A decreased Glomerular Filtration Rate (GFR) is defined as less than 60 ml/min/1.73m^2. Staging of CKD is based on the GFR categories created by the KDIGO guidelines, thus a patient diagnosed to have kidney failure is categorized

as CKD G5 with a GFR of < 15 ml/min/1.73 m^2.[80] The label “pre-dialysis”, although not officially defined in guidelines, are given to patients with GFR < 15-20 ml/min/1.73m^2, with a decline in renal function, and an expected start of dialysis within 6-12 months.[81]

Clinical Question 9. Among patients with CKD, what is the level of blood pressure to start pharmacotherapy to prevent cardiovascular complications and renal progression?

Statement 9: Patients with blood pressure* more than or equal to 140/90 mmHg should have prompt initiation and timely titration of pharmacotherapy to achieve blood pressure goals.

This recommendation is shared among the KDIGO[78], JNC 8[82] and the ADA Standards of Medical Care – 2019 guidelines[53]. Evidence forwarded include randomized controlled trials that have unequivocally demonstrated that treatment of hypertension to blood pressure < 140/90 mmHg reduces cardiovascular events as well as microvascular complications. Elevated levels of blood pressure especially >150mmHg systolic, are linearly related to increases in kidney disease progression and a higher incidence of cardiovascular events in patients with diabetes.[53.78.82-83]

Clinical Question 10. Among adult patients with CKD who are pre-dialysis, what is the target blood pressure to prevent cardiovascular complications and renal progression?

Statements:

10.1 . For *routine office blood pressure measurement*, maintain a BP target consistently less than 140 mmHg systolic and less than 90 mmHg diastolic in patients with low risk of cardiovascular disease and CKD grade 4 and 5, or if with adverse effect on intensive target of less than 130/80 mmHg. CKD patients with high cardiovascular risk or CKD grade 3 or earlier is recommended to have a blood pressure target of less than 130/80 mmHg.

10.2. A systolic BP of **less than 120 mmHg** using a *standardized office BP measurement* is targeted, when tolerated, among adults with high BP and non-dialysis CKD.

We recommended an **individualized treatment target** for the following patient populations: Diabetic Kidney Disease patients, CKD grade 4 and 5 not in dialysis patients, patients with proteinuria of more than 1 g/day, individuals with baseline SBP of 120 to 129 mmHg, those with very low diastolic BP of less than 50 mmHg with CAD, those with white

coat or severe hypertension, stroke patients, those with age less than 50 with low absolute risk for CV disease or those individuals above 90 years of age, very frail patients, those with limited life expectancy and those with symptomatic postural hypotension.

10.3. If unable to obtain a standardized BP measure, maintain a blood pressure target consistently less than or equal to 130 mmHg systolic and less than or equal to 80 mmHg diastolic in patients with urine albumin excretion of more than 30 mg per 24 hours unless adverse event occurs with achievement of this target.

This target blood pressure was forwarded by all guidelines with some variations. The KDIGO[78] accepts targets equal to 140mmHg systolic and 90mmHg diastolic, but JNC[82] and ADA[53] places targets below these marks. The KDIGO further qualifies that this target be set among diabetic kidney disease patients whose urinary albumin excretion does not exceed 30mg per 24 hours (or its equivalent). Randomized controlled trials available at the time have been consistent in suggesting that lowering blood pressure so that it is consistently less than 140/90 mmHg will prevent major cardiovascular events. Lowering blood pressure to these levels is also likely to reduce the risk of progressive chronic kidney disease.[78]

Recently both KDOQI and KDIGO put out new publications in view of the recent hypertension guidelines from the ESC/ESH[6] and AHA/ACC[5]. KDOQI publish a US commentary on the 2017 ACC/AHA hypertension guideline. It stated that based on a new meta-analysis it seems reasonable to target a BP of less than 130/80 from G1 to G3B CKD. For patients with CKD G4 and G5, there are insufficient data to modify the target BP.[79]

This more intensive target was forwarded by both KDIGO[78] and the ADA Standards of Medical Care[53]. KDIGO qualifies patients with urine albumin excretion of more than 30 mg per 24 hours (or equivalent) and whose blood pressure is consistently above 130 mmHg systolic or above 80 mmHg diastolic be treated to this target goal. Their bases are mainly from observational studies that show level of urine albumin predicts risk for adverse cardiovascular and kidney outcomes and that blood pressure lowering reduces the rate of urinary albumin excretion, which may in turn lead to a reduced risk of both kidney and cardiovascular events. KDIGO sites the Steno Diabetes Center in Copenhagen RCT study (Steno-2) as its reference for this recommendation, aside from various observational studies.[78]

The ADA Standards of Medical Care recommends this target for patients with higher risk of cardiovascular events (either with ASCVD or with ASCVD score > 15%)[53]. The strongest direct evidence the group presented was from the Action to Control Cardiovascular Risk in Diabetes blood pressure (ACCORD BP)[63] with regards the benefits and the risk targeting this more intensive blood pressure control. Additional studies such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Hypertension Optimal Treatment (HOT) trial[62], also examined the effects of intensive versus standard control, but the relevance of their results to people with diabetes is less clear (with SPRINT altogether excluding patients with diabetes in its population). The ADA Standards of Medical Care – 2019 also did meta-analyses of trials to clarify optimal blood pressure targets with diabetes and found out that treating patients with baseline blood pressure more than or equal to 140 to targets less than 140 mmHg is beneficial, while more intensive targets may offer additional though less robust benefits. [53]

Potential side effects of antihypertensive therapy were taken into consideration in both guidelines. Hypotension, syncope, acute kidney injury and electrolyte abnormalities are among the side effects most seen in various studies targeting this more intensive blood pressure goal. The latter patients should have their goal targets reset to the standard target level instead.

Clinical Question 11. Among adult patients with CKD, what is the level of blood pressure to start initiation with two antihypertensive drugs to prevent cardiovascular complications and renal progression?

Statement 11. Patients with confirmed office-based blood pressure of more than or equal to 160/100 mmHg should, in addition to lifestyle modification, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events.

The ADA Standards of Medical Care[53] recommends those with blood pressure more than or equal to 160/100 mmHg pharmacotherapy with two antihypertensive medications in order to effectively achieve adequate blood pressure control. Single-pill antihypertensive combination may improve compliance in this scenario. For patients with blood pressure between 140/90 mmHg to 159/99 mmHg, single drug regimen may be initially given.[53]

As the mechanisms for most CKD patients' hypertension are a mixed of volume dependent (or water retention), renin-dependent type of hypertension. A two-drug combination should consider these mechanisms in the choice of anti-hypertensive. Generally regarded to address volume dependent type of hypertension are calcium channel blockers and diuretics and ACE, ARB, and beta blockers for the renin dependent type.

Clinical Question 12. Among adult patients with CKD, what is the anti-hypertensive of choice to prevent cardiovascular complications and renal progression?

Statement 12. Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with CKD such as ACE inhibitors, Angiotensin Receptor Blockers, Thiazide-like diuretics, and dihydropyridine calcium channel blockers.

Initial treatment for hypertension should include medications that have been proven to reduce cardiovascular events. Several trials have already proven the effectiveness of ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics and dihydropyridine calcium channel blockers in decreasing cardiovascular events. The ADA Standards of Medical Care [53] refers to works from a systemic meta-analysis by Catala-Lopez et. al. and another by Palmer et. al. besides findings from ALLHAT Collaborative Research Group and ACCOMPLISH investigators.[53]

The use of ACE-inhibitors and ARB among CKD may be associated with increase in the level of creatinine and potassium. Persistent elevation of creatinine and potassium should prompt referral to a specialist.

Clinical Question 13. Among adult patients with CKD with albuminuria/proteinuria, what is the anti-hypertensive of choice to prevent cardiovascular complications and renal progression?

Statement

13.1. An ACE inhibitor or Angiotensin receptor blocker, at maximally tolerated dose is the recommended first-line treatment for hypertension in CKD patients with urinary albumin-to-creatinine ratio more than or equal to 30 mg/g (or equivalent). If one class is not tolerated, the

other is substituted. **These medications should not be discontinued unless serum creatinine level rise above 30 % over baseline during the first two months of treatment or hyperkalemia (serum potassium level > or = 5.6 mmol/L).** If the patient is intolerant to both ACE inhibitor and angiotensin receptor blocker, we prefer a non-dihydropyridine calcium channel blocker (verapamil or diltiazem) be used as first line treatment in this setting.

13.2. Combinations of ACE inhibitor and Angiotensin receptor blocker, and of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should NOT be used.

KDIGO recommends an ARB or an ACE-I be used in adults with diabetes and CKD with urine albumin excretion of KDIGO Grade 2 albuminuria of 30 – 300 mg per 24 hours (or equivalent)[78]. The trials involved mainly diabetic patients with microalbuminuria and showed effect on surrogate outcomes, most commonly the transition to overt proteinuria; none demonstrated conclusively that these improvements are associated with a reduction of hard end points. KDIGO, however, recommends utilization of ACE-I or ARB in diabetics with CKD with urine albumin excretion more than 300 mg per 24 hours (KDIGO Grade 3 albuminuria) or equivalent There was strong evidence conducted in patients with diabetes and CKD demonstrating that ACE-I and ARB protect against kidney failure and increase in albumin levels.[78]

The choice between ACE-I and ARB in CKD patients is controversial. In general, the evidence for kidney outcomes supports the use of ACE-I is older and applies largely to type 1 diabetes, whereas evidence supporting ARB use comes from more recent trials in type 2 diabetes. For cardiovascular protection in patients with diabetes, the evidence largely points to ACE-I. The available data are consistent, suggesting the effects of both classes of agents are likely similar.[78]

Non-dihydropyridine calcium channel blockers, diltiazem and verapamil, may be used as first-line therapy in patients intolerant of ACE inhibitors or ARBs, or as second line agents in combination with an ACE inhibitor or ARB in CKD patients in reducing proteinuria.[83] These agents may reduce higher-level albuminuria without a RAAS blocker, but in combination with an ACE inhibitor or ARB, they help to reduce blood pressure while preserving kidney function in people with diabetes.[84] Dihydropyridine CCBs, such as amlodipine and nifedipine, are effective antihypertensive agents but do not reduce proteinuria and may cause dose-dependent peripheral edema effect. They should only be used in conjunction with a RAAS blocker for BP lowering.[84]

Trial data clearly demonstrate a lack of benefit and an increased risk of harm, manifested by hyperkalemia and acute kidney injury, in using a combination RAAS blockade approach[85]. The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study found an increased risk of hyperkalemia and acute kidney injury and did not show any benefit on mortality and cardiovascular events.[86] The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) found combination therapy of two RAAS blockers to be associated with more adverse events without further reduction in cardiovascular or renal events.[87] Finally, the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) where a direct renin inhibitor plus an ACE-inhibitor combination was used ended prematurely because of higher renal and cardiovascular event rates in the combination arm.[88]

Clinical Question 14. Among adult patients with CKD and resistant hypertension, is addition of mineralocorticoid receptor antagonist beneficial in reducing albuminuria and cardiovascular events?

Statement 14. CKD patients with resistant hypertension not meeting blood pressure targets on three classes of anti-hypertensive medications (including diuretic) should be considered for mineralocorticoid receptor antagonist therapy.

Resistant hypertension is defined as BP that remains above target despite the concurrent use of three or more antihypertensive medications of different classes, one of the agents should be a diuretic, and all the drugs that are prescribed are at maximum tolerated doses[5,6,8].
Mineralocorticoid receptor antagonists (MRA) are effective management of resistant hypertension in patients with type 2 diabetes when added to existing triple regimen.[53,83] The use of MRA also reduces albuminuria and have additional cardiovascular benefits. However, the risk of hyperkalemia increases when these agents are added to a regimen that has an ACE-inhibitor or ARB included. Therefore, regular monitoring of potassium levels as well as serum creatinine cannot be overemphasized in this setting according to ADA Standards of Medical Care.[53] Persistent elevation of blood pressure, hyperkalemia and creatinine should prompt referral to specific subspecialty.

Clinical Question 15. Among adult patients with CKD, is giving anti-hypertensive at bedtime more beneficial in reducing cardiovascular event?

Statement 15. Administer one or more antihypertensive medications at bedtime

There is growing evidence that suggests that there is an association between the absence of nocturnal blood pressure dipping and the incidence of ASCVD. This recommendation was first introduced in the ADA Standards of Medical Care Guidelines.[53] Unfortunately, there was just one randomized controlled by Hermida et al in 2011 that showed this benefit of better blood pressure control and decreased cardiovascular events.[89] In the present ADA Standards of Medical Care – 2019, another paper by Zhao et al was quoted that further substantiated this benefit of administering medications in the evening.[90]

There is also a practical advantage of giving anti-hypertensive at bedtime especially for patients on dialysis. Some patients may also be prone to hypotension during dialysis which usually happen at daytime. In addition, some anti-hypertensive agents are dialyzable.

III. Blood Pressure Management in Persons with Stroke

The relationship between hypertension and stroke is very dynamic and multifaceted. Management of hypertension during the acute onset of stroke (may it be ischemic or hemorrhagic) and during the secondary prevention phase pose a challenge due to the intricacies of how elevated blood pressure (BP) control must be handled.

Clinical Question 16.1 For adults with acute ischemic stroke (AIS) who are eligible for intravenous (IV) thrombolysis but not for mechanical thrombectomy, what is the threshold for pharmacological treatment and the target blood pressure (BP)?

Statement 16.1 For adults with AIS who are eligible for IV thrombolysis but not for mechanical thrombectomy, it is recommended that the BP be maintained <185/110 mmHg prior to treatment and during infusion. For the next 24 hours after treatment, the BP is recommended to be maintained <180/105 mmHg.

Clinical Question 16.2 For adults with AIS who are eligible for IV thrombolysis but not for mechanical thrombectomy, what are the pharmacologic agents of choice to reach the target BP?

Statement 16.2 It is recommended to use a titratable intravenous medication to allow adjustment of the drug depending on the current BP. For patients with acute ischemic stroke otherwise eligible for intravenous thrombolysis with BP >185/110 mmHg before or during infusion, or BP >180/105 mmHg after treatment, the recommended pharmacologic agent is Nicardipine 5mg/hr IV, titrate up by 2.5mg/hr every 5-15 minutes, with maximum of 15mg/hr. If available, labetalol 10 mg IV over 1-2 minutes followed by continuous IV infusion of 2-8 mg/min may also be used.

The blood pressure thresholds were largely from the National Institute of Neurologic Disorders (NINDS) t-PA trial[91,92], and was subsequently validated by other trials, studies, and registries that show higher BP significantly increased the risk of hemorrhagic transformation. Analysis of the SITS-ISTR (Retrospective Analysis From Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register)[93] showed a linear relationship between blood pressure elevation and symptomatic hemorrhage. However, blood pressure fluctuations must also be avoided as these are associated with adverse events like larger infarct size, intracranial hemorrhage, and worse outcomes.

The BP threshold recommendations promote perfusion to the ischemic territories while mitigating potential risks of intracranial hemorrhage. This has been adapted and recommended by treatment guidelines in different countries including the American Heart Association/American Stroke Association (AHA/ASA)[91], European Stroke Organization (ESO)[92], National Institute for Healthcare and Excellence (NICE)[94], and Canadian Stroke Best Practice Recommendation[95].
There is limited data in the choice of BP lowering medication for acute ischemic stroke. In IV alteplase trial protocols, some suggestions regarding medications are given and shown on the following table.[91]

Table 5. Options to Treat Hypertension in Patients with Acute Ischemic Stroke (AIS)

Patient eligible for emergency reperfusion except that BP > 185/110 mmHg
Nicardipine 5 mg/IV, titrate up by 2.5 mg/hr every 5-15 min, max 15 mg/hr, adjust BP
Other agents (eg: hydralazine, enalaprilat) may also be considered
If BP is not maintained to $\leq$ 185/110 mmHg, do not consider alteplase
Management of BP during and after alteplase or other emergency reperfusion therapy
Monitor BP every 15 min for 2 hours from the start of alteplase, then every 30 min for 6 hours, then every hour for 16 hours

If systolic >180-230 mmHg or diastolic BP > 105 – 120 mmHg
Nicardipine 5 mg/hr IV, titrate up to desired effect by 2.5 mg/hr every 5-15 min, max 15 mg/h
If BP not controlled or diastolic BP > 140 mmHg, consider IV sodium nitroprusside

Clinical Question 17.1. For adults with AIS who are eligible for mechanical thrombectomy (with or without IV thrombolysis), what is the threshold for pharmacological treatment and the target BP?

Statement 17.1. In patients for whom mechanical thrombectomy is planned, it is reasonable to maintain BP <185/110 mmHg before, during, and after the procedure. After the procedure, the target BP depends on the recanalization status, with lower BP thresholds recommended for those with successful recanalization and reperfusion.

There is a paucity of prospective studies and trials which determine the target BP prior, during, and after endovascular treatment for acute ischemic stroke. Most recommendations are derived from registries, retrospective studies, or secondary analysis of the thrombectomy trials. Aside from the ESCAPE trial, all thrombectomy studies used a BP cut – off of 185/110 mmHg and this has been adapted by some guidelines[96]. The vast majority of patients enrolled in <6-hour RCTs received IV alteplase, and the trial protocols stipulated management according to local guidelines with BP ≤180/105 mmHg during and for 24 hours after the procedure for these participants.[91] The ESCAPE protocol states that SBP ≥150 mmHg is probably useful in promoting and keeping collateral flow adequate while the artery remains occluded and that controlling BP once reperfusion has been achieved and aiming for a normal BP for that individual is sensible. It is reasonable to use this level as of now, until additional data becomes more available. The AHA/ASA and the ESO recommends similar thresholds with intravenous thrombolysis, with lower targets in case of complete reperfusion[96-97]. What this “lower” target is unknown as of now. Owing to the scarcity of data, it is left to the judgment of the operating interventionist and attending neurologist to determine which BP levels to maintain.

Goyal et al.[98] published a single center’s experience with different BP targets following endovascular therapy over 4 years. Following good reperfusion, patients were either assigned to permissive (<220/110 mmHg or 180/110 mmHg if IV t-PA also administered), moderate (<160/90 mmHg) or intensive (<140/90 mmHg) BP targets in a non-randomized fashion. While patients in the moderate and intensive groups received antihypertensive agents more frequently, the 3-

month mortality rate in these groups was significantly lower (6.5%) compared to those with a permissive threshold (28.7%). This study provides evidence that a lower BP threshold may be beneficial in patients who have achieved good recanalization status. It may be reasonable to target a lower BP goal for patients with excellent reperfusion (TICI 2b/3) and minimal infarct volume. In cases where there is incomplete or poor reperfusion, substantially less data exists to help guide management.[96]

Clinical Question 17.2 For adults with AIS who are not eligible for IV thrombolysis or mechanical thrombectomy, what pharmacological agent may be used to achieve target BP, when needed?

Statement 17.2: For adults with AIS who are not eligible for IV thrombolysis or mechanical thrombectomy, the use of IV nicardipine to achieve the target BP may be considered.

Clinical Question 18.1. For adult patients with acute hypertensive parenchymal intracerebral hemorrhage (ICH), what is the threshold for BP lowering in the first few hours upon presentation at the emergency room?

Statement 18.1 For adult patients with acute ICH, the threshold for BP lowering is SBP ≥ 180 mmHg.

Clinical question 18.2. What would be the target BP when lowering the blood pressure in acute Intracerebral hemorrhage (ICH)?

Statement 18.2 The target SBP is <180 mm Hg. In patients with SBP ≥180 mm Hg, careful BP lowering to 140 to 160 mm Hg should be considered. The magnitude of BP reduction is dependent on the clinical context. It should be careful SBP lowering (avoiding reductions ≥60mmHg in 1 h). It is also recommended to keep the blood pressure stable and avoid variability. Likewise, it is also recommended not to lower the BP acutely to <140mmHg

In adult patients with acute ICH, elevated BP is common in the acute setting due to several factors which include stress, pain, elevated intracranial pressure, and history of an acute or continuous increase in BP[106-107]. Sustained elevated BP has been shown in some studies to contribute to early enlargement of hematoma and worsening of neurologic condition. [2,3] In the 6th edition of the

Stroke Society Handbook for Stroke Prevention, and Rehabilitation in 2014, it was recommended that treating hypertension if SBP >180 mmHg and lowering it to 140 mmHg within 7 days is safe and improves outcome in patients with small to moderate-sized ICH not requiring surgical intervention[109] This recommendation was based mainly on the INTERACT- 2 Trial published in 2013.[110] The INTERACT 2 Trial is one of the largest RCT in looking at early aggressive lowering of BP within the first 6 hours of ICH stroke onset. In 2015, the AHA/ASA released the recommendation that for patients with ICH presenting with BP of between 150-220 mmHg and without contraindication to acute BP treatment, acute lowering of BP to 140 mmHg is safe and can be effective in improving functional outcome[111]

However, findings from Antihypertensive Treatment of Acute Cerebral Hemorrhage ATACH-2 Trial published in 2016[112] and its subsequent analysis in 2018 led to more uncertainty as to how fast should SBP be lowered in the early hours of stroke onset. The proportions of deterioration within 24 h were considerably greater in patients with reduced and sustained SBP of <140 mmHg. There were higher proportions of cardiac-related complications within 7 days among patients with reduction and maintenance of SBP <140 mmHg.[113]

Because of persistent uncertainty whether intensive systolic blood pressure lowering in acute cerebral hemorrhage is beneficial for the patient, especially with regards to the timing, target, and intensity of systolic blood lowering, a combined analysis of both INTERACT 2 and ATACH 2 trials would help answer those uncertainties.[114] Looking at these two large RCT trials together, no measurable benefit to lowering SBP to <140 mmHg was demonstrated in the acute phase of ICH. There is no clear-cut target SBP trial evidence if any, above 140 mmHg. All current trials have followed the convention in limiting SBP increases beyond 180 mmHg.

The Individual Participant Data Analysis of the 2 large RCTs (INTERACT -2 and ATACH-2) showed that depending on the clinical context, the target BP may be between 140-160 mmHg. In mild to moderate severity ICH achieving levels as low as SBP 120-130 mmHg may be optimal for improved functional outcome in ICH of mild to moderate severity.

The 2017 ACC/AHA Guidelines as well as the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension are however both in agreement with the following similar recommendations[5-6] In the ESC/ESH patients with acute intracerebral hemorrhage, immediate BP lowering is

not recommended for patients with SBP <220 mmHg; In patients with SBP ≥ 220 mmHg, careful acute BP lowering with IV therapy to <180 mmHg should be considered.[6]

In the ACC/AHA guidelines, adults with ICH who present with SBP >220 mmHg, it is reasonable to use continuous IV drug infusion and close BP monitoring to lower SBP. Immediate lowering of SBP to <140 mm Hg in adults with ICH who present within 6 hours and have a SBP 150-220 mmHg is not beneficial to reduce death or severe disability and can potentially be harmful[5] In the latest 2020 Hypertension Canada Guidelines, the following recommendation is stated: For patients with ICH in the hyperacute phase, SBP lowering to <140 mmHg should be avoided due to an absence of benefit relative to a target BP of <180 mmHg (Grade A;new guideline) some suggestion of harm.[12]

Clinical Question 18.3 What are the pharmacologic agents of choice and manner of administration among adult patients with acute ischemic stroke?

Statement 18.3. It is recommended to use intravenous antihypertensive agents that can easily be titrated to lower the BP to the desired level. The 1st line drug of choice is IV Nicardipine. Alternative treatment choice would be labetalol, when available.

In adult patients with AIS who are not eligible for IV thrombolysis or mechanical thrombectomy and without serious co-morbid condition, elevations in BP of <220/120 mmHg should not be routinely treated. A drastic BP reduction could result in sequelae such as progression of stroke and acute kidney injury - both resulting from compromised cerebral and renal perfusion, respectively.[99] A MAP of 110 to 130 mmHg must be maintained to improve cerebral perfusion pressure. While MAP can only be measured directly by invasive monitoring, this can be estimated using the formula: MAP = 1/3 (SBP – DBP) + DBP where SBP is the Systolic BP and DBP is the Diastolic BP. The benefit of initiating or resuming treatment for hypertension within the first 48 to 72 hours in patients with AIS is still uncertain, however, it is said to be safe but is not effective in improving stroke outcomes including prevention of death or dependency. In the CATIS trial[100], although the mean BP was significantly lower among the intervention group, early antihypertensive treatment was not associated with significant reduction in the risk of death or disability at either 14 days or 3 months after inclusion in the study. The conclusion is that unless the SBP is >220 mmHg, there is no evidence to treat BP in AIS if the goal is to improve stroke outcomes. In a meta-regression study[101], it was shown that significant decrease in blood pressure

during the early ischemic stroke period results in increased risk of death and of combined death/dependency.

However, in AIS patients with severe hypertension of SBP ≥220 mmHg or DBP ≥120 mmHg or with concomitant serious medical issues such as acute coronary event, acute heart failure, aortic dissection, post-fibrinolysis symptomatic intracerebral hemorrhage, or preeclampsia/eclampsia, it is reasonable to initiate hypertension medications to reduce the BP by approximately 15% but not more than 25% (with close monitoring) within the first 24 hours and gradually reduce then after.[102-104] The choice of pharmacological agents and route of administration must not cause a precipitous drop in the BP. In the Philippine setting, the use of IV nicardipine is reasonable as it is readily available, titratable, has a short duration of action, and has no significant effect on the intracranial pressure. Nicardipine may be given at 5 mg/h IV infusion as initial dose and titrated by 2.5 mg/h every 5 minutes to a maximum of 15 mg/h to achieve the target BP as recommended.[102] For stable patients who remain hypertensive at ≥140/90 mmHg) for more than 3 days after AIS, initiation or resuming anti-hypertensive medications should be considered.[105]

Clinical Question 19. For adults who have a history of stroke, what is the target blood pressure level for secondary prevention?

Statement 19. For adults with history of stroke, the target blood pressure level for secondary prevention is less than or equal to 130/80 mm Hg. RAS blockers, CCBs and thiazide diuretics remain to be the first-line pharmacologic agents in hypertension management for secondary stroke prevention.

A patient with a history of stroke will most likely have another stroke in his lifetime, with recurrent strokes making up almost 25% of nearly 800,000 strokes annually[115]. Hypertension remains to be the most important risk factor for both ischemic and hemorrhagic strokes. Therefore, adequate BP control plays a significant role in secondary stroke prevention. Patients with previous strokes are among the high-risk population groups together with those who have diabetes, heart failure and chronic kidney disease.

Globally, various national medical organizations have released updated guidelines on the target BP levels for secondary prevention. Some guidelines exhibited similarities as well as substantive differences with one another. ISH 2020[9], ACC/AHA 2017[5], JSH 2019[40] and Chinese 2018[33] guidelines have recommended <130/80 mm Hg as the target BP level for patients with previous stroke.

The ESC/ESH 2019 hypertension guideline recommends a BP treatment threshold of DBP ≥90 or SBP ≥140 mm Hg with ultimate treatment targets being < 130/80 mm Hg; among those < 65 years, the SBP target is 120–129 mm Hg while in patients 65 and older, the target is 130–139 systolic.[6] The Hypertension Canada 2018 guidelines recommend pharmacologic treatment to be initiated in patients with macrovascular target organ damage or other CVD risk factors when average DBP is ≥90 or SBP ≥140 mm Hg; target BP levels are < 140/90 mm Hg.[38] The NHF Australia 2016 guidelines recommend that all those requiring antihypertensive treatment should be treated to a primary target of <140 mm Hg systolic, including those with a history of chronic kidney disease, peripheral vascular disease, stroke, and diabetes mellitus. However, in selected high (>15%; 5-year risk) CVD risk populations including those diabetic subjects in whom stroke prevention is prioritized and those with chronic kidney disease, a secondary target of <120 mm Hg systolic can be considered.[36]

RAAS blockers, CCBs and thiazide diuretics remain to be the first-line pharmacologic agents in hypertension management for secondary stroke prevention.[9]

Table 6. Summary of Blood Pressure Thresholds and Targets for Persons with Stroke

Context	BP threshold for initiating pharmacotherapy	Blood Pressure Targets	Preferred Agents
In-hospital Mgt	Refer to Neurologist for specialist management		Intravenous titratable anti-hypertensives
Acute Ischemic Stroke (AIS), eligible for IV thrombolysis but not for mechanical thrombectomy	>185/110 mmHg	<185/110 mmHg prior to thrombolysis and during infusion; <180/105 mmHg in the next 24 hours	Nicardipine 1-5mg/hr IV, titrate up by 2.5mg/hr every 5-15 minutes, with maximum of 15mg/hr. If available: alternative of labetalol 10 mg IV over 1-2 mins

			followed by continuous IV infusion of 2-8 mg/min.
AIS, not eligible for IV thrombolysis or mechanical thrombectomy	Severe hypertension: SBP of >220 mm Hg DBP of >120 mm Hg	If with severe hypertension, reduce the BP by 15% during the first 24 hours after the onset of stroke	IV Nicardipine as indicated above
Intracerebral Hemorrhage (ICH)	SBP ≥180 mmHg	<180 mmHg Careful SBP lowering, avoiding reductions ≥60 mmHg in 1 hour Do not lower the BP acutely to< 140 mmHg	First choice: IV Nicardipine Second choice: IV labetalol
Secondary prevention Adults with history of stroke	140/90 mm Hg	≤130/80 mmHg	First line: RAS blockers (ACE-Inh, ARB), CCBs and thiazide diuretics

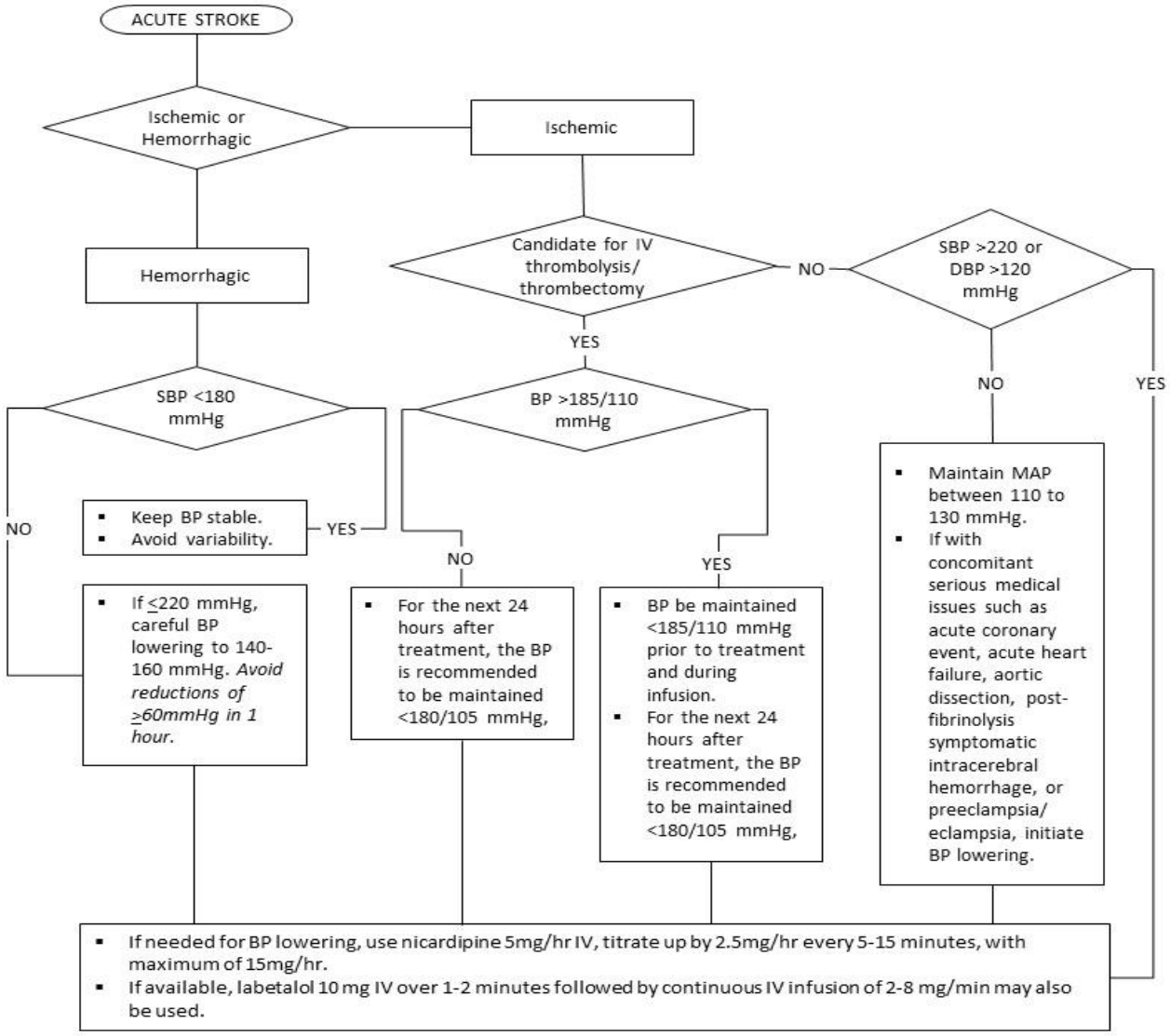


Figure 3: Algorithm for Blood Pressure Management at the Emergency Room in Acute Stroke Patients

IV. Blood Pressure Management in Pregnancy

Hypertensive disorders of pregnancy (HDP) constitute one of the major causes of maternal and perinatal morbidity and mortality worldwide. It has been estimated that preeclampsia complicates 2-8% of all pregnancies globally[116]. In the Philippines, HDP account for 36.7% of all maternal deaths[117] and remains as the second leading cause of maternal mortality from 1991-2006 according to the data culled from the Department of Health[117] which is much higher that the worldwide rate of 18% according to the WHO[118-119].

Hypertensive disorders of pregnancy can be subclassified into four groups- Chronic hypertension, Gestational hypertension, preeclampsia and superimposed preeclampsia in the setting of chronic hypertension as presented in the American College of Obstetricians and Gynecologists (ACOG) Guideline in 2013[120]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has published guidelines on diagnosis to establish global unity of definition in referring to the various hypertensive disorders seen in pregnancy, with the most recent guideline released in 2018 which includes the category of White coat hypertension and Masked hypertension[121].

Although each condition increases the risk of maternal and neonatal morbidity, the greatest risks are associated with a diagnosis of preeclampsia, either de novo or in the setting of chronic hypertension.[122-123] Women with a history of preeclampsia have an elevated risk of cardiovascular disease in subsequent years. Preeclamspia has been linked by several systematic reviews and meta-analyses to the development of cardiovascular disease (hypertension, myocardial infarction, congestive heart failure), cerebrovascular events (stroke), peripheral vascular disease and cardiovascular mortality later in life.[122-123]It is postulated that endothelial dysfunction, which has been linked to atherosclerosis, persists in women with a history of preeclampsia, years after an affected pregnancy[122].

Clinical Question 20. What are the different types of hypertensive disorders of pregnancy (HDP) and what are the criteria for each?

1. Pre-eclampsia- Elevated blood pressure **and** proteinuria.
    1.1 Elevated blood pressure defined as
        1.1.1 Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure.
        1.1.2 Systolic blood pressure of 160 mm Hg or more diastolic blood pressure of 110 m Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).
    1.2 Proteinuria
        1.2.1 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection), or
        1.2.2 Protein/creatinine ratio of 0.3 mg/dl or more or
        1.2.3 Dipstick reading of 2+ (used only if other quantitative methods not available)
    1.3 Or in the absence of proteinuria, new onset hypertension with the new onset of any of the following:
        1.3.1 Thrombocytopenia: Platelet count less than 100,000 x 10^9/L
        1.3.2 Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
        1.3.3 Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
        1.3.4 Pulmonary edema
        1.3.5 New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

2. Eclampsia- New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use.

3. Chronic Hypertension- Hypertension of any cause that predates pregnancy. BP $\geq$ 140/90 mm Hg before pregnancy or before 20 weeks gestation or both.

4. Chronic Hypertension with Superimposed Pre-eclampsia- Chronic hypertension in association with preeclampsia. Others define it as worsening baseline hypertension accompanied by new-onset proteinuria or other findings supportive of preeclampsia.

Table 7. Classification of Hypertension of Pregnancy[124-128]

Hypertensive Disorder of Pregnancy (HDP)	Criteria
Preeclampsia	Blood Pressure ● Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure. ● Systolic blood pressure of 160 mm Hg or more diastolic blood pressure of 110 m Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy). And Proteinuria ● 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or ● Protein/creatinine ratio of 0.3 mg/dl or more or ● Dipstick reading of 2+ (used only if other quantitative methods not available) Or in the absence of proteinuria, new onset hypertension with the new onset of any of the following: ● Thrombocytopenia: Platelet count less than 100,000 x 10^9/L ● Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease ● Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration ● Pulmonary edema New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Eclampsia	• New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use.
Chronic Hypertension	• Hypertension of any cause that predates pregnancy. BP $\geq$ 140/90 mm Hg before pregnancy or before 20 weeks gestation or both.
Superimposed preeclampsia	• Chronic hypertension in association with preeclampsia. Others define it as worsening baseline hypertension accompanied by new-onset proteinuria or other findings supportive of preeclampsia.
Gestational Hypertension	• Systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure. • Hypertension without proteinuria or severe features develops after 20 weeks of gestation and blood pressure levels return to normal in the postpartum period (12 weeks postpartum).

Table 8. Indicators for Severe Pre-eclampsia[124-128]

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count < 100,000 x 10^9/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit normal concentration), and severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses.
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Clinical Question 21. What blood pressure criteria is used to define hypertension in pregnancy?

Statement 21 Hypertension is diagnosed empirically when appropriately taken blood pressure exceeds 140 mm Hg systolic or 90 mm Hg diastolic. Korotkoff phase V is used to define diastolic pressure.

Previously, incremental increases of 30 mm Hg systolic or 15 mm Hg diastolic above blood pressure values taken mid-pregnancy were used as diagnostic criteria, even when absolute values were < 140/90 mm Hg. These incremental changes are no longer used to define hypertension, but it is recommended that such women be observed more closely[124].

Clinical Question 22. What antihypertensive agents can be used for urgent blood pressure control in pregnancy?

Statement 22. Acute-onset severe hypertension (systolic BP of 160 mm Hg or more or diastolic BP of 110 mm Hg or more, or both) can occur in the prenatal, intrapartum and postpartum period. It is accurately measured using standard techniques and is persistent for 15 minutes or more. The first line of treatment is intravenous (IV) hydralazine and labetalol; intravenous nicardipine is also an option. Extended release oral nifedipine also may be considered as a first line therapy, particularly when IV access is not available. Use of these drugs does not require cardiac monitoring[129].

The objectives of treating severe hypertension are to prevent congestive heart failure, myocardial ischemia, renal injury or failure, and ischemic or hemorrhagic stroke.[129] The available literature suggests that antihypertensive agents should be administered within 30– 60 minutes. However, it is recommended to administer antihypertensive therapy as soon as reasonably possible after the criteria for acute-onset severe hypertension are met. The goal of treatment is not to normalize BP, but to achieve a range of 140-15-/90-100 mmHg in order to prevent repeated, prolonged exposure to severe systolic hypertension, with subsequent loss of cerebral vasculature auto-regulation. Maternal stabilization should be done before delivery. When acute onset, severe hypertension is diagnosed in the office setting, the patient should be expeditiously sent to the hospital for treatment.

A recent Cochrane systematic review that involved 3,573 women found no significant differences regarding either efficacy or safety between hydralazine and labetalol or between hydralazine and calcium channel blockers. Thus, any of these agents can be used to treat acute severe hypertension in pregnancy[130]. Although parenteral antihypertensive therapy may be needed initially for acute control of blood pressure, oral medications can be used as expectant management is continued. One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/d). If the maximum dose is inadequate to achieve the desired blood pressure goal, or the dosage is limited by adverse effect, then short-acting oral nifedipine can be added gradually. The extended release nifedipine 30 mg oral tablet is an effective antihypertensive agent that is less likely to result in a rapid and severe fall in blood pressure than the immediate release capsule and provides antihypertensive effects over several hours. [131]

Options for second-line therapy includes nicardipine by infusion pump[132]. A review of studies of intravenous nicardipine for treatment of severe hypertension in pregnancy found that target blood pressure was reached within 23 minutes in 70 percent of pregnant patients with severe hypertension and 91 percent reached target blood pressure within 130 minutes, with no severe maternal or fetal side effects.[133]

Table 10. Antihypertensive agents for urgent blood pressure control in pregnancy[134-135]

DRUG	INITIAL DOSE	FOLLOW-UP DOSE
Hydralazine	5 mg IV gradually over 1 to 2 minutes. Adequate reduction of blood pressure is less predictable than with IV labetalol	Repeat BP measurement at 20-minute intervals: If BP remains above target level at 20 minutes, give 5 or 10 mg IV over 2 minutes, depending on the initial response. If BP remains above target level at 40 minutes, give 10 mg IV over 2 minutes, depending on the previous response. Cumulative maximum dose is 30 mg. If target BP is not achieved, switch to another class of agent.

Nicardipine (parenteral)	The initial dose is 5 mg/hour IV by infusion pump and can be increased to a maximum of 15 mg/hour. Onset of action is delayed by 5 to 15 minutes; in general, rapid titration is avoided to minimize risk of overshooting dose. Requires use of a programmable infusion pump and continuous noninvasive monitoring of blood pressure and heart rate.	Adjust dose within this range to achieve target BP.
Nifedipine extended release	30 mg orally	If target BP is not achieved in 1 to 2 hours, another dose can be administered. If target BP is not achieved, switch to another class of agent. ***Maximum daily dose is 180 mg***
Nifedipine immediate release*	10 mg orally May be associated with precipitous drops in BP in some women, with associated FHR decelerations for which emergency cesarean delivery may be indicated. As such, this regimen is not typically used as a first-line option and is usually reserved only for women without IV access. If used, FHR should be monitored while administering short-acting nifedipine.	Repeat BP measurement at 20-minute intervals: If BP remains above target at 20 minutes, give 10 or 20 mg orally, depending on the initial response. If BP remains above target at 40 minutes, give 10 or 20 mg orally, depending on the previous response. If target BP is not achieved, switch to another class of agent. ***Maximum daily dose is 180 mg***

*NOTE: We caution against use of immediate-release oral nifedipine, although some obstetric guidelines have endorsed its use as a first-line option for emergency treatment of acute, severe hypertension in pregnancy or postpartum (other options were labetalol and hydralazine), particularly when IV access is not in place. In most cases, use of immediate-release oral nifedipine will be safe and well tolerated; however, there is a risk of an acute, precipitous fall in blood pressure, which may result in a reduction in utero-placental perfusion. The immediate-release preparations are also associated with a higher incidence of headache and tachycardia. In non-pregnant adults, the package insert states that "nifedipine capsules should not be used for the acute reduction of blood pressure."

Clinical Question 23. When do we treat hypertension during pregnancy?

Statement 23 Treatment of severe hypertension (blood pressure of ≥160/100mmHg) is always recommended as it prevents serious maternal and fetal complications to set in. Initiating therapy in non-severe disease, however, is a subject of controversy.

The NICE, ISSHP and SOGC recommends therapy when the blood pressure remains above 140/90 mmHg, but SOGC suggests a lower threshold in patients with other co-morbidities. (21,24,25,26) The ACOG recommends conservative management of non-severe disease but stressed on the importance of control in the severe type.[136]

A judicious approach to the treatment of mild (blood pressure of 140-150 mmHg/90-100 mmHg) to moderate (blood pressure of 150-159 mmHg/100-109 mmHg) hypertension is made with consideration on the patient's co-morbidities and symptoms (eg, headaches, visual disturbances).

The goal of antihypertensive therapy during pregnancy is not to normalize the blood pressure, but to achieve a value that would prevent repeated prolonged exposure to severe systolic hypertension, with subsequent loss of cerebral vasculature autoregulation. It is important to avoid hypotension because the degree by which placental blood flow is auto-regulated is not established, and aggressive lowering may cause fetal distress.[121] The Canadian guidelines[137] recommend 130-150/90-105 mmHg in the absence of co-morbid conditions. The NICE guidelines[138] recommend aiming for 135/85 mmHg or less. The ISSHP endorses an approach that seeks to control blood pressure levels to 110-140/85 mmHg[121].

Clinical Question 24. What are the pharmacologic treatment options?

Statement 24: The choice of antihypertensive drug for initial therapy should be based on the characteristics of the patient, contraindications to a particular drug and physician and patient preferences. The first line drugs are methyldopa, calcium channel blockers or beta blockers. Antihypertensives may be used to keep systolic blood pressure at 130 to 155 mmHg and diastolic blood pressure at 80 to 105 mmHg.

In a 2014 Cochrane Collaboration systematic review, antihypertensive medication use for non-severe hypertension in pregnancy (49 randomized trials; n ¼ 4723) was associated with a halving in the risk of progression to severe hypertension (relative risk, 0.49; 95% CI, 0.40-0.60). The number needed to treat was 10 (95% CI, 8-13). This finding was consistent across all HDP ranges of conditions[139].

Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral methyldopa, long-acting oral nifedipine, or other oral beta blockers (acebutolol, metoprolol, pindolol, and propranolol[140]. A diastolic blood pressure of 85 mm Hg should be targeted for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension. A similar target could be considered for pregnant women with preeclampsia.

Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be from a different drug class chosen from first-line or second line options[141].

Table 11: Antihypertensive medications commonly used in pregnancy

First line oral drugs (Grade C)	Second line oral drugs (Grade D)	Medications to avoid
• Methyldopa • Long acting oral nifedipine • Other beta blockers (acebutolol, metoprolol, pindolol and propranolol)	• Clonidine • Thiazide diuretics	• Angiotensin converting enzyme inhibitors* (Category X) • Angiotensin receptor blockers* (Category X)

* Fetotoxicity of renal system

Category X: Studies in animals or humans have demonstrated teratogenic effects. The risk to the fetusclearly outweighs any potential benefit to the mother. Drugs in this category are contraindicated in pregnancy.

For patients with chronic hypertension, It can be difficult to differentiate worsening of the hypertension from superimposed preeclampsia. Conditions that may indicate superimposed preeclampsia, that warrants a referral to a maternal fetal medicine specialist/perinatologist, include the following:

1) Acute, severe, and persistent elevations in blood pressure.
2) Sudden increase in baseline hypertension.
3) New-onset proteinuria or sudden increase in proteinuria (above the threshold for normal or a clear change from baseline).

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should NOT be given before conception and during the first trimester of pregnancy because of evidence of teratogenicity (ACE inhibitor exposure increased the risk for cardiovascular and central nervous system anomalies). Likewise, they should NOT be used during the second and third trimesters of pregnancy because of evidence of fetopathy (fetal and neonatal death, renal failure, oligohydramnios, arterial hypertension, intrauterine growth restriction, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria and limb defects)[142].

Clinical Question 25: How is hypertension managed during the immediate postpartum and breastfeeding periods?

Statement 25: Blood pressure should be recorded shortly after birth and if normal, again within 6 hours.

All women should have BP recorded and discharge deferred for at least 24 hours or until vital signs are normal and/or treated or referred. Any woman with an obstetric complication and/or newborn with complications should stay in the hospital until both are stable[143].

- In hospital stay for at least 24 hours
- Checkup within 48-72 hours of the birth and again 7-14 days and at six weeks post-partum.
- All women should be reminded of the danger signs of preeclampsia following birth including headaches, visual disturbances, nausea, vomiting, epigastric or hypochondrial pain, feeling faint or convulsions.

VI. Blood Pressure Management in the Pediatric Population

Clinical Question 26. Among pediatric patients, what is the threshold for commencing pharmacologic treatment for Hypertension?

Statements:

26.1. Pharmacologic treatment for hypertension (HTN) should be started for children with the following conditions:

- 26.1.1 Children who remain hypertensive even after six (6) months of lifestyle modification strategies* (see Table 1);
- 26.1.2 Symptomatic hypertension or Stage 2 hypertension;
- 26.1.3 Presence of co-morbidities like chronic kidney disease (CKD) or diabetes mellitus (DM), or any evidence of target organ involvement (e.g. left ventricular hypertrophy).

26.2. The goal of pharmacologic therapy **should be a reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) to <90th percentile for age, sex and height and <120/80 mm Hg in adolescents ≥13 years of age.**

26.3. For children with CKD, BP targets should be less than or equal to 50th percentile for age, sex and height.

26.4 The goal of treatment of hypertension in the pediatric population is not only to reduce BP to <90th percentile for age, sex and height and <130/80 mm Hg, but also to reduce cardiovascular risk factors, and prevent target organ damage.

26.5 Follow-up every **4-6 weeks** is recommended for monitoring and evaluation of therapy.

The goal of pharmacologic and non-pharmacologic treatment of HTN in pediatric population for both primary and secondary is not only to reduce BP to <90th percentile and <130/80 mm Hg, but also to reduce the risk for HTN, target organ damage and other related cardiovascular related disease in adulthood.[144]

Different studies showed that children with elevated BP are more likely to develop HTN in adulthood, compared to children with low BP.[145] There is evidence showing that lowering BP to <90th percentile lowers the risk of left ventricular hypertrophy (LVH) and decreases left ventricular mass index (LVMI).[144] Therefore, the recommended goal is to lower BP to <90th percentile or <130/80 mm Hg, whichever is lower, during treatment of HTN in children.

Blood pressure control in patients with CKD significantly delays the progression of renal disease.[146] As cited in the KDIGO guideline of 2012, the evidence of this came from the ESCAPE trial which showed that by targeting 24-hour MAP by ABPM to less than the 50th percentile for age, height and sex showed benefit in slowing CKD progression and the effect was stronger in proteinuric children with CKD. It is known that dyslipidemias and HTN are risk factors for future CVD subclinical atherosclerosis.[144,147] The incidence of HTN in patients with DM type 1 is between 6% and 16%. [148] HTN is a modifiable cardiovascular risk factor that maybe undiagnosed or under-treated, particularly in children with type 1 diabetes.[144,146] Studies show that one of the risk factors for the development of HTN in adulthood is obesity. Severe obesity (BMI 95th-98th percentiles) has a four-fold risk of development of HTN compared to normal-weight children. The higher the BP during infancy, the higher the risk of developing HTN in adulthood.[144]

Lifestyle change and pharmacologic treatment can significantly control BP. Adult studies have shown that lifestyle modification results in good BP control and decrease the cardiovascular mortality. The established dietary strategy in the control of HTN is the DASH approach, and specific elements of that diet have been described. Physical activity and exercise are beneficial in lowering BP as well. A review of 9 studies of physical activity interventions in children and adolescents with obesity suggested that 40 minutes of moderate to vigorous, aerobic physical activity at least 3 to 5 days per week, improved SBP by an average of 6.6 mm Hg and prevented vascular dysfunction.

Table 12. Blood Pressure Stages in Filipino Pediatric Population

Filipino Children 1–13 y	Filipino Children ≥ 13 y
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg
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 mmHg, 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

Clinical Question 27. What advice regarding nonpharmacologic treatment is recommended for pediatric patients?

Statements

27.1 Non-pharmacologic therapy of lifestyle modification which includes Dietary Approaches to Stop Hypertension (DASH) and engaging in 30-60 minutes of moderate to vigorous physical activity at least 3-5 days a week should be initiated in all pediatric patients consulting for the first time for HTN.

27.2 All children diagnosed to have HTN should be screened for other cardiovascular risk factors including obesity by checking their body mass index (BMI) during each child visit.

27.3 Weight loss intervention is recommended for identified overweight and obese children until a normal BMI is attained through dietary counselling and exercise (weight loss of 1 to 2 kg per month).

27.4 All children diagnosed to have HTN or elevated BP should be advised to decrease intake of calorie-dense food and beverages, and those with high sodium content. They should be advised to increase intake of fruits and vegetable to 3-5 servings per day.

27.5 All children diagnosed to have HTN should be advised to engage in moderate-to-vigorous exercise 30 - 60 mins at least 3-5 times a week and preferably daily, unless with medical contraindication.

27.5.1 All children diagnosed to have HTN should be advised to avoid smoking including electronic cigarettes and exposure to tobacco smoke.

27.5.2 All children diagnosed to have HTN should be advised to avoid alcohol intake and caffeinated energy drinks.

Summary of Evidence:

Lifestyle interventions are recommended to lower BP. Studies of hypertensive youth suggest that the relationship between diet, physical activity, and BP in childhood is similar to that observed in adults.

BMI Interpretation

Interpretation of Cut-Offs (WHO Reference 2007)[149]

Overweight – more than +1 SD (equivalent to BMI 25kg/m^2 at 19 years)

Obesity – more than + 2 SD (equivalent to BMI 30kg/m^2 at 19 years)

Interpretation based on Centers for Disease Control and Prevention 2000[150]

Overweight – BMI between the 85th to 94th percentile

Obesity – BMI more than or equal to 95th percentile

Weight loss intervention

In overweight children, weight reduction is associated with a decrease in office BP[10] and is the primary therapy for obesity related HTN. It has been demonstrated that lifestyle interventions incorporating a dietary component along with exercise or behavioral therapy can lead to improvements in both weight and cardiometabolic factors, including BP.[151] A meta-analysis of randomized controlled trials found that a net weight reduction of 5.1 kg (95% CI 4.25 to 6.03 kg), resulting from restricted energy intake, increased physical activity or both, reduced SBP by 4.44 mmHg (95% CI 2.95 to 5.93 mmHg) and DBP by 3.57 mmHg (95% CI 2.25 to 4.88 mmHg).[152] The long-term benefit of weight reduction on BP control has been confirmed in several studies, including Phase II of the Trials of Hypertension Prevention Collaborative Research Group.

DASH approach

The DASH approach includes a diet that is high in fruits, vegetables, low fat milk products, whole grains, fish, poultry, nuts, and lean red meats; it also includes a limited intake of sugar and sweets along with lower sodium intake.

Prospective studies have shown the effects of diet on lifetime BP. Consumption of more than one serving of dairy products/day and more than two servings of fruits and vegetables/day throughout adolescence have shown to lead to about a 35% lower risk of elevated BP.[153] Likewise, saturated fat-reduced diet since infancy decreases BP.[154] Higher sugar sweetened beverage consumption is associated with higher SBP in adolescents.

The healthy food plate for Filipinos also known as PINGGANG PINOY is a food guide using a food plate model to show the recommended proportion by food group in every meal. It gives recommendation on the amount of GO (energy giving), GROW (body building), and GLOW (body regulating) foods for all age groups divided into the Kids (ages 3 -12 yo), Teens (ages 13 -18 yo), adults (ages19 - 59 yo) older adults (ages 60 yo and above) and pregnant women. It is a visual tool which may be used to educate families on healthy eating habits and presented on a per-meal basis.It answers the question of how much you should eat in on meal in order to be healthy.[154] The contents of PinggangPinoy is nutritionally sound and in congruence with the DASH approach. The Pinggang Pinoy may be downloaded from the FNRI website[154]

High salt intake in children and adolescents is positively correlated with high SBP and an elevated risk of HTN, and a meta-analysis has shown that a 3 g/day reduction of salt intake leads to a decrease in SBP and DBP of 1.2/1.3mmHg.[155] Starting in newborns, a 15-year follow-up study has suggested a predictive role of the effect of salt intake in early life on BP.[156] Excessive salt intake seems to be not only linked with BP elevation but also with other cardiovascular risk factors as salt produces a reduction in vascular nitric oxide bioavailability that limits endothelium-dependent dilation.[157] The World Health Organization (WHO)stated that the recommended maximum intake of salt for adults be adjusted downward for children aged two to 15 years based on their energy requirements relative to those of adults. This recommendation for children does not address the period of exclusive breastfeeding (0–6 months) or the period of complementary feeding with continued breastfeeding (6–24 months). *But recent recommendation from the Canadian Pediatric Society, states that the AI (adequate intake) for sodium in children and youth*

aged 1 to 18 years should be extrapolated from the adult AI of 1,500 mg/day, using average estimated energy requirements for different groups. It is recommended that the sodium consumed should be iodized or "fortified" with iodine, which is essential for healthy brain development in the fetus and young child and optimizing people's mental function in general.[158] Based on the recommendation of FNRI the limit of sodium intake per day is <2 grams in adults. [154]

Exercise

Observational data support a relationship between physical activity and lower BP. Interventional data demonstrate increasing physical activity leads to lower BP. A review of 9 studies of physical activity interventions in children and adolescents with obesity suggested that 40 minutes of moderate to vigorous, aerobic physical activity at least 3 to 5 days per week improved SBP by an average of 6.6 mm Hg and prevented vascular dysfunction.[159] A more recent analysis of 12 randomized controlled trials including 1266 subjects found reductions of 1% and 3% for resting SBP and DBP, respectively.[146] Any type of exercise, whether it's aerobic training, resistance training, or combined training, appears to be beneficial.[21] Programs that combine diet and physical activity can have a beneficial effect on SBP, as is shown in several studies designed to prevent childhood obesity and address cardiometabolic risk.

Based on the WHO, the recommended physical activity of children aged 5 – 17 years old is at least 60 minutes of accumulated moderate to vigorous physical activities daily. [158]

Parents should be instructed to limit sedentary time such as screen time (TV, gadgets, smartphones). Screen time recommendations include a maximum of 2 hours screen time for children more than 5 years of age, less than 1 hour for children 2-5 years, and no screen time for less than 2 years of age. [160]

Avoid exposure to tobacco smoke and electronic (e')-cigarettes

Environmental exposure to tobacco is an important risk factor contributing to the development and severity of CVD. The heart and vascular system are highly vulnerable to tobacco smoking. Discouraging maternal smoking and maintaining a strictly smoke-free environment are of great importance because of the accumulating evidence on the importance of fetal and early life factors in determining cardiovascular risk. In adolescents, promotion of smoke-free rules at home may help prevent the uptake of cigarettes. Although in active smokers, cessation of smoking is

mandatory to improve cardiovascular risk due to the acute pressor effect that may raise daytime ambulatory BP.[6]

Aside from the traditional tobacco products such as cigars or cigarettes the tobacco industry has progressed to develop other alternative products due to the decline in tobacco usage. The e'-cigarettes is a device that heats a liquid containing nicotine and flavors to form aerosol for inhalation. Children and adolescents should be educated on the harmful effects of using these products due to the direct effects on their general and cardiovascular health. An experimental study has shown that vaping e'-cigarette causes a significant increase in BP which lasted about 30 minutes and accompanied by acute increase in heart rate.[23]Nicotine in conventional cigarettes as well as in e'-cigarettes increase the risk of CVD such as acute coronary disease, HTN and heart failure.[161]

Clinical Question 28. What are the BP targets for prevention of target organ complications?

Statements

28.1 The target BP for children is <90th percentile for age, sex and height or <120/<80 mmHg whichever is lower.

28.2 For CKD patients, BP target may need to be less than or equal to 50th percentile for age, sex and height as long as there are no signs or symptoms of hypotension.

There are still no data to identify a specific level of BP in childhood that leads to adverse CV outcomes in adulthood. The previous recommendations for HTN treatment target in children without CKD or diabetes were SBP and DBP<95th percentile. Since that recommendation was made, evidence has emerged that markers of target organ damage, such as increased LVMI, can be detected among some children with BP >90th percentile(or >120/80 mm Hg) but <95thpercentile.[161-163] Longitudinal studies on BP from childhood to adulthood that include indirect measures of CV injury indicate that the risk for subsequent CVD in early adulthood increases as the BP level in adolescence exceeds 120/80mm Hg.[164-165] In addition, there is some evidence that targeting a BP<90th percentile results in reduction sin LVMI and prevalence of LVH.[31]Therefore, an optimal BP level to be achieved with treatment of childhood HTN is <90th percentile or <130/80mm Hg, whichever is lower.

New normative BP tables based on normal-weight children are available in the 2017 AAP guideline that included SBP and DBP values arranged by age, sex, and height (and height percentile). However, full BP tables are complicated and leads to under recognition thus the simplified BP table was created for initial BP screening. This is based on the 90th percentile BP for age and sex of the children at the 5th percentile of height.[144]

Clinical Question 29. What are the preferred medications for children?

29.1 Any of the following drugs may be used as initial treatment for children with hypertension: ACE inhibitors (Enalapril, Captopril), ARBs (Losartan, Valsartan), or calcium channel blockers (Amlodipine).

29.2 For children with co-existing chronic kidney disease, proteinuria or diabetes mellitus, an ACE-inhibitor or ARB is recommended as the initial antihypertensive drug unless with absolute contraindications. Referral to a specialist is highly recommended.

29.3 Therapy should start with a single drug at the lowest possible dose and titrated up every 2 to 4 weeks until target BP is achieved, or the maximal dose is reached or adverse effects occur.

29.4 If BP is not controlled with a single agent (maximal dose is reached or adverse effects occur), a second agent can be added to the regimen and titrated as with the initial drug. Because the use of other anti-hypertensive agents can lead to compensatory salt and water retention, the addition of a thiazide diuretic to an initial drug for uncontrolled hypertension is prudent.

29.5 In combining agents from different drug classes, it is preferable to give those with complementary modes of action. Ideally, no two drugs which act separately on the RAAS, should be used in combination because of the risk of hyperkalemia, impaired kidney function and hypotension.

ACE inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), long-acting calcium channel blockers (CCBs), and Beta Blockers are the most studied antihypertensive agents in the pediatric population.[167-170] However, head to head trial of efficacy of these drugs in children are limited. Long-term studies on safety and future Cardiovascular disease impact of these drugs are also lacking. Based on studies comparing ACEIs, ARBs, and long-acting CCBs in terms of BP lowering, none has been proven to be significantly superior over another. No dose-response

relationship has likewise been clearly demonstrated. However, beta-blockers have more adverse effects and are not associated with improved outcomes in adults; hence favoring ACE, ARBs, and long-acting CCBs as initial drugs for pediatric hypertension[167-169].

Monotherapy starting at a low dose, and careful titration every 2-4 weeks until the maximum dose is reached, the target BP is attained, or adverse effects have developed is recommended. Follow-up during titration is best to monitor drug effects. However, if proper home BP measurement can be done, follow up can be every 4-6 weeks. If a second agent is necessary to achieve target BP, a thiazide diuretic is recommended to offset the salt and water retention that can ensue as compensatory mechanism for the effect of the initial drug. Ideally, no two drugs acting on the Renin-angiotensin-aldosterone system (RAAS) should be combined to avoid increase in similar adverse effects particularly hyperkalemia, and impaired kidney function.

Drugs that have been proven efficacious in children and approved by the FDA should be used[170]. More importantly, the recommended drugs per drug group are available here in the Philippines and are included in the Essential Medicines List by the Department of Health. This means that these drugs were assessed to be cost-effective and that their prices are being regulated[171]. Losartan, Valsartan, Enalapril, and Amlodipine are such drugs. Captopril, has a long history of use in children. Although no well designed pediatric trial has been, its safety profile, the class effect of ACEIs, and its low cost explain the recommendation. Other drugs approved for use in children, those with a history of safety in children, and belonging to recommended drug groups may however, still be used.

A Cochrane review of antihypertensive agents[168] showed that although calcium channel blockers are very commonly prescribed antihypertensive agents in pediatric patients, the evidence for their blood pressure-lowering efficacy is limited. But there is not enough evidence to favor ARB, and ACEI over a CCB. The results of the analyses are not robust enough to provide firm recommendations for first-line agents in children with hypertension from primary or secondary causes. There is a suggestion, however, that those medications that act through the renin-angiotensin pathway may lower blood pressure more than other pharmacological interventions. Amlodipine was found efficacious in a study by Flynn et al.[152]

ACEIs and ARBs are contraindicated in pregnancy. Female hypertensives in childbearing age must be warned and can be given the option to take a long-acting calcium channel blocker or a beta-blocker. Hypertensive children with associated CKD, DM, or proteinuria should be initially started on ACEI or ARB unless with absolute contraindication. Absolute contraindication includes bilateral renal artery stenosis, angioedema, pregnancy, and hypersensitivity reaction to the drug. Potassium levels must be monitored and treated accordingly.

Starting a new drug for a patient must always be done judiciously making sure there is no contraindication to use and with advise for precautions and monitoring for adverse drug reactions. At each follow up visit, assessment for adherence to prescribed therapy must be done including assessment of drug adverse effects and target organ damage. Laboratory testing as deemed necessary should be requested.

The pharmacologic treatment of acute severe hypertension in children is mainly based on studies in adults, though there are some clinical trials and case series in the pediatric population.[154] Emergent acute drug therapy is necessary to prevent target organ damage (TOD) if the BP is more than 20% of the Stage 2 hypertension limit, or at least 30 mmHg above the 95th percentile, or the patient shows sign of hypertension-related acute TOD like encephalopathy, kidney injury, or heart failure. A secondary cause of hypertension must always be ruled out in these cases. The BP must be reduced immediately but no more than 25% of target BP over 6-8 hours, then gradual reduction over the next 24 hours. Rapid decrease in BP may compromise perfusion of vital organs (brain, kidney).

Clinical Question 30: What is the recommended technique and BP device for accurate BP measurement in pediatric patients?

Statements

30.1 The use of proper technique and appropriately-sized cuff is critical for the accurate measurement of BP in children.

30.2 An auscultatory device using an aneroid non-mercury sphygmomanometer is recommended for children.

30.3 An oscillometric device is a suitable alternative to auscultation for initial BP screening and monitoring in the pediatric population.

30.4 Ambulatory BP monitoring (ABPM) is recommended in children (> 5 years old) and adolescents with the following conditions:

30.4.1 Elevated office BP measurements for 1 or more years, or if with stage 1 hypertension over 3 clinic visits, for confirmation of hypertension.

30.4.2 Those with high-risk conditions (e.g. obesity, CKD or structural renal abnormalities, diabetes mellitus, those who have undergone solid organ transplant, obstructive sleep apnea, repaired aortic coarctation) to document masked hypertension.

30.4.3 Those with *suspected* white coat hypertension (WCH).

30.5 Home BP monitoring should not be used to diagnose hypertension, MH, or WCH but may be a useful adjunct to office and ambulatory BP measurement if clinically validated oscillometric apparatus and appropriate-sized cuffs are used.

Unlike in adults which only uses a standard adult cuff, the use of different appropriate sizes of cuff for the children's upper arm is important.[167-168] Small cuffs tend to overestimate while large cuffs underestimate BP readings.

The American Heart Association advises clinicians to have the following cuff sizes on hand: newborn/ premature infant (4 cm X 8 cm), infant (6cm X 12 cm), older child (9 cm X 18 cm), standard adult, large adult and thigh for leg measurement or for children with large arms. [1,] The bladder width of the cuff should be 40% of the patient's arm circumference at a point midway between the olecranon and the acromion process and should cover 80 – 100 % of the circumference of the arm. [167-168]

The child should be calm and relaxed in a quiet environment. When possible, patient should be seated with their right arm resting at heart level and his/her feet on the floor, not dangling from the examiner's table. The patient's legs should be uncrossed, with the back and arm supported. A cuff placed over clothing can cause a 5 – 10 discrepancy in SBP, an unsupported back can cause a 6 – 10 mmHg discrepancy in SBP, and sitting with the arm unsupported can cause a 1 – 7 mmHg in SBP and 5 -11 mmHg discrepancy in DBP. The examiner should also avoid talking during measurement, since talking and active listening can cause a 10-mmHg discrepancy in SBP and DBP.[168]

The systolic blood pressure is defined by the first Korotkoff sound (K1) whereas diastolic blood pressure coincides with the disappearance of the pulse (K5). [168] When selecting a device, clinicians must consider the necessary equipment, advantage and disadvantages associated with each option.

AUSCULTATORY DEVICE

The "gold standard" method to measure BP in children is auscultation using a mercury sphygmomanometer which are comparable,[167-169] however, due to concerns about toxicity of mercury, using an aneroid non-mercury manometer is a more environment friendly alternative.

To increase accuracy, aneroid devices need regular calibration (every six months) and units should preferably be wall-mounted units for them to be less likely to be dropped or subject to trauma.[168] At least three measurements performed on different occasions are necessary for the diagnosis of hypertension. Target organ damage (such as increased LV mass and elevated PWV) was best predicted by BPs obtained by auscultation.[169]

OSCILLOMETRIC DEVICE

The use of oscillometric (automated) devices in clinical practice has increased with the following advantages: ease of use than sphygmomanometer, ecologically friendly, less susceptible to error and bias, easier to use when auscultation is challenging, beneficial in situations when frequent measurement is necessary and cuff placement is less critical.[3,4] However, there are wide variations in oscillometric devices which need appropriately sized cuffs and need to be validated prior their use in children. Studies also demonstrated that oscillometric devices systematically **overestimate** SBP (by 10 mmHg) and DBP (by 5 mmHg) compared with values obtained by auscultation leading to misclassification of BP status.[170]

A diagnosis of hypertension based on an oscillometric measurement should be confirmed by an auscultatory method.[3] If the initial BP is elevated (≥90th percentile), providers should perform 2 additional oscillometric or auscultatory BP measurements at the same visit and average them. If using auscultation, this averaged measurement is used to determine the child's BP category (i.e, normal, elevated BP, stage 1 HTN, or stage 2 HTN). If the averaged oscillometric reading is ≥90th percentile, 2 auscultatory measurements should be taken and averaged to define the BP category.[168]

Serial office oscillometric measurements are preferred than single office oscillometric measurement since effects of white-coat HTN and masked HTN are reduced.

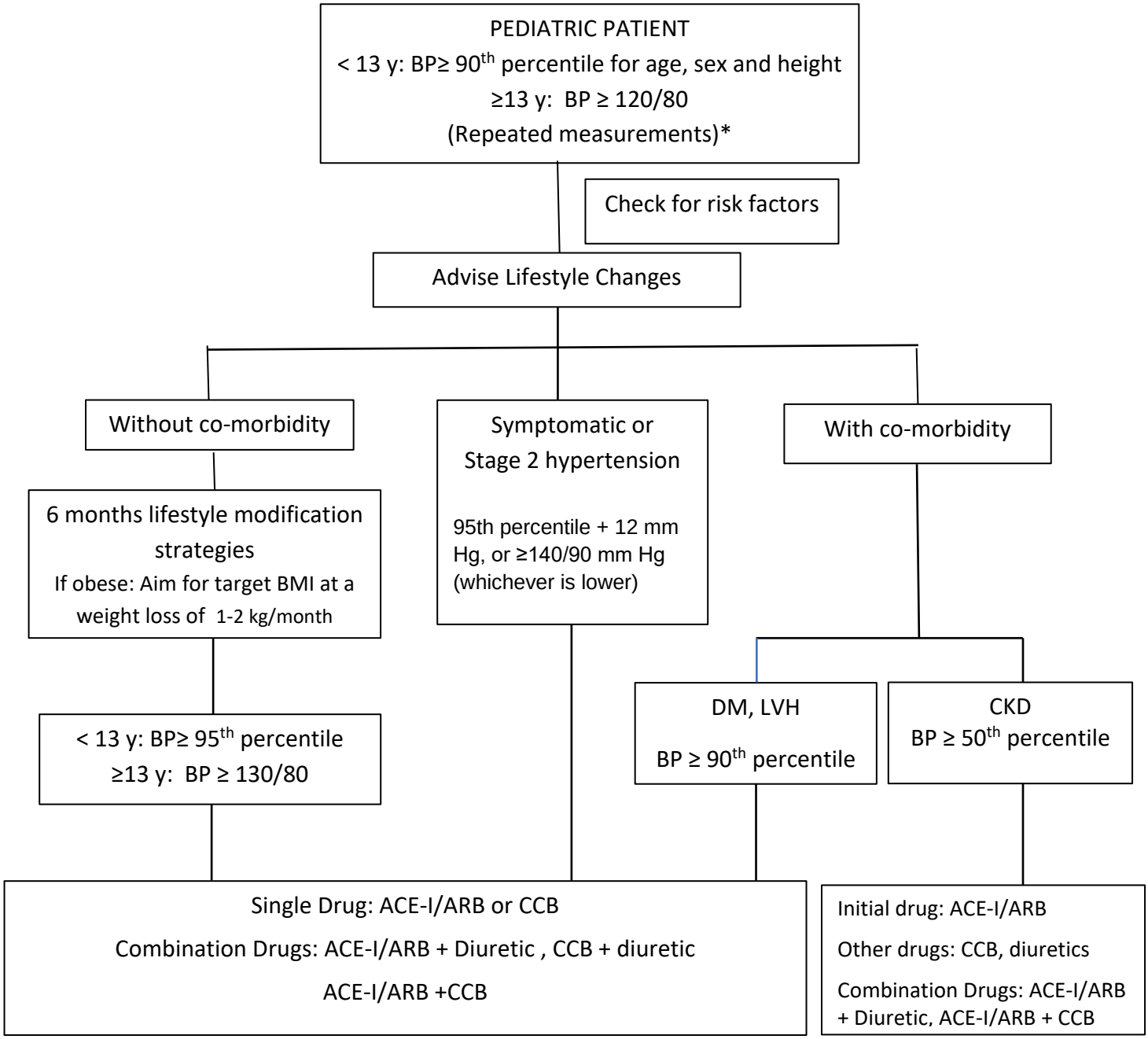
AMBULATORY BP MONITORING (ABPM)

The current use of ambulatory BP monitoring (ABPM) in pediatrics is limited due to its cost, accessibility and presence of gaps in knowledge of its indications. Furthermore, it may not be well tolerated in children, requires family training and cooperation and may be susceptible to misreporting. Likewise, there are currently no uniform normative values for sex, height or race.[1, 3]

Current literature shows the following benefits of ABPM in children:[171]

(1) more accurate for the diagnosis of HTN than clinic BP measurement
(2) more predictive of future BP and can assist in the detection of secondary HTN
(3) increased left ventricular mass index and left ventricular hypertrophy correlate more strongly with ABPM parameters than casual BP
(4) ABPM is more reproducible than casual or home BP measurement.

The major benefits of ABPM are the following: it allows to identify “white coat hypertension” (elevated office BP values and normal ABPM values which is presence of mean SBP and DBP < 95th percentile and SBP and DBP load <25% on ABPM), “masked hypertension” (normal office BP values and elevated ABPM values) and subjects with or without reduced physiological day-night blood pressure variations (dipping).[6] Load is defined as the percentage of valid ambulatory BP measurements above set threshold values (eg. >95th percentile) for age, sex and height.



*If initial BP is elevated, two additional measurements must be performed and averaged

Figure 5. Treatment Algorithm for Hypertension in the Pediatric Population

Limitations of the Guidelines

The process in creating this 2020 Clinical Practice Guidelines has limitations. The use of ADAPTE method enabled us to compare the different guidelines created by other medical societies all over the world, and to utilize the evidence that are available through the published guidelines. While the process allows the TWG to retrieve, assess and evaluate the individual clinical trials and studies that were used to generate these guideline recommendations, we did not do the systematic literature search for individual studies ourselves. Thus, there may have been newly published or available information which may have been missed in the process of guideline development. There were also limited Filipino data, particularly in the pediatric population. We encourage Filipino researchers and physicians to conduct more local clinical trials and epidemiologic studies.

CONCLUSIONS

The clinical questions and statements in this clinical practice guideline allow us to holistically manage the Filipino hypertensive individual. We recommend that BP should be equal or more than 140/90 mmHg to be diagnosed as hypertensive. The target BP threshold should be less than 130/80 mmHg to prevent hypertensive mediated organ damage. We also recommend that lifestyle modification be advised to all hypertensive patients. The use of appropriate anti-hypertensive medications depending on the co-morbidity of the individual is recommended. We also recommended management for the pediatric and the pregnant hypertensive. Simplified algorithms are provided to serve as a quick reference guide to clinicians.

The 2020 CPG is designed to be a guide for clinicians in managing hypertension for the Filipino patient. This, however, should not replace sound clinical judgment by doctors and the ultimate decision for treatment should involve both clinician and the patient.